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SNPs in PTGS2 and LTA Predict Pain and Quality of Life in Long Term Lung Cancer Survivors

Sarah M. Rausch, Ph.D.[*,1], **Brian D. Gonzalez, M.A.**[1], **Matthew M. Clark, Ph.D.**[2], **Christi Patten, Ph.D.**[2], **Sara Felten, B.S.**[2], **Heshan Liu, M.S.**[2], **Yafei Li, PhD**[2], **Jeff Sloan, Ph.D.**[2], and **Ping Yang, M.D., Ph.D.**[2]

Sarah M. Rausch: sarah.rausch@moffitt.org; Brian D. Gonzalez: Brian.gonzalez@moffitt.org; Matthew M. Clark: Clark.matthew@mayo.edu; Christi Patten: Patten.christi@mayo.edu; Sara Felten: Felten.sara@mayo.edu; Heshan Liu: Liu.heshan@mayo.edu; Yafei Li: li.yafei@mayo.edu; Jeff Sloan: Sloan.jeff@mayo.edu; Ping Yang: Yang.ping@mayo.edu

[1]Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, Tampa, FL 33612

[2]Mayo Clinic, 200 First St SW, Rochester, MN 55905

Abstract

PURPOSE—Lung cancer survivors report the lowest quality of life relative to other cancer survivors. Pain is one of the most devastating, persistent, and incapacitating symptoms for lung cancer survivors. Prevalence rates vary with 80–100% of survivors experiencing cancer pain and healthcare costs are five times higher in cancer survivors with uncontrolled pain. Cancer pain often has a considerable impact on quality of life among cancer patients and cancer survivors. Therefore, early identification, and treatment is important. Although recent studies have suggested a relationship between single nucleotide polymorphisms (SNPs) in several cytokine and inflammation genes with cancer prognosis, associations with cancer pain are not clear. Therefore, the primary aim of this study was to identify SNPs related to pain in long term lung cancer survivors.

PATIENTS AND METHODS—Participants were enrolled in the Mayo Clinic Lung Cancer Cohort upon diagnosis of their lung cancer. 1149 Caucasian lung cancer survivors, (440 surviving < 3 years; 354 surviving 3–5 years; and 355 surviving> 5 years) completed study questionnaires and had genetic samples available. Ten SNPS from PTGS2 and LTA genes were selected based on the serum literature. Outcomes included pain, and quality of life as measured by the SF-8.

RESULTS—Of the 10 SNPs evaluated in LTA and PTGS2 genes, 3 were associated with pain severity (rs5277; rs1799964), social function (rs5277) and mental health (rs5275). These results suggested both specificity and consistency of these inflammatory gene SNPs in predicting pain severity in long term lung cancer survivors.

[*]Corresponding Author: Sarah M. Rausch, PhD, Phone: (813) 745-2194, Fax: (813) 745-3906, Sarah.Rausch@moffitt.org.

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CONCLUSION—These results provide support for genetic predisposition to pain severity and may aid in identification of lung cancer survivors at high risk for morbidity and poor QOL.

Keywords

genetics; SNPs; pain; quality of life; lung cancer; cytokines; LTA; PTGS2

INTRODUCTION

Lung Cancer and Pain

Lung cancer remains the leading cause of cancer death worldwide.[1] Unfortunately, despite widespread advances in detection and treatment, survival rates remain low [2]. Therefore, primary goals of treatment include reducing symptom burden and improving quality of life (QOL) [3]. However, there is a paucity of longitudinal research on survivors compared with those in active treatment. [4]Lung cancer patients report the lowest quality of life relative to other cancer survivors [3,5]. Quality of life is associated with symptom burden and with survival in lung cancer patients, [5] and pain significantly contributes to diminished QOL in lung cancer survivors. [3,6,7]

Pain is one of the most common, and distressing symptoms reported by patients with cancer throughout the disease and treatment trajectories. [8–14] As many as 90% of patients with cancer experience pain during the course of their illness,[8] and 60–80% report experiencing moderate to severe pain.[9,10] Despite the high frequency and clinical importance, up to 45% of cancer patients have inadequate and undermanaged pain control, [11,12] and 40% of 5-year survivors report cancer pain. [15] In fact, pain has been reported as the most distressing symptom in cancer patients [13,14,16] and has a considerable impact on QOL among cancer patients and survivors. [6,7]

Many patients endure pain in the survivorship phase, often as a result of the treatment received. Although the etiology of cancer pain is unclear, several proposed mechanisms include primary activation of visceral or somatic nociceptors by a tumor, impingement of tumor on adjacent tissue, obstruction of blood vessels, chemotherapeutic agents, damage to nervous system, thoracotomy, and inflammation caused by cytokines. [17]

Cancer-related chronic pain remains a poorly explored survivorship issue. [15] The number of cancer survivors in the United States has more than tripled to around 10 million people over the past 30 years. [2] Despite relatively low survival rates, 26,000 individuals become long-term lung cancer survivors each year. [2] Unfortunately, chronic pain in cancer survivors is a poorly studied and understood entity. [17] Currently, there are no models to predict pain in cancer patients, and thus no personalized approaches to the treatment and management of this important clinical outcome.

Inflammation pathways and cancer symptoms

Increasing evidence consistently supports the role of pro-inflammatory mediators in the mechanism of cancer pain.[18] Although there are many mechanisms accounting for the pain experience, inflammatory networks likely are central mechanisms within cancer

populations. The mechanisms of multidimensional psychobehavioral-neuroendocrine-immune system interactions, including the bidirectional influence of inflammation on morbidity factors in immunologically moderated diseases such as cancer are beginning to be understood.

Higher levels of circulating inflammatory markers, including cytokines, have been reported to be independent predictors of shorter overall survival, event-free survival, and complete remission rates in a number of cancers.[19] Interestingly, inflammatory markers have also been emerging as predictors of cancer symptom burden and quality of life (QOL). Cytokines have been associated with fatigue in breast cancer survivors,[20] depressive symptoms in mixed cancer patients,[21–23] and increased symptom burden among non-small cell lung cancer patients,[24] QOL in hematological cancer patients,[25] pain, fatigue, poor appetite, insomnia, anxiety, and dyspnea among cancer patients with cachexia.[26]

Although the exact molecular mechanisms by which cytokines influence pain is not fully elucidated, studies suggest that cytokines released during inflammation or tissue damage (as in the cancer process) modify activity of nociceptors contributing to pain hypersensitivity. Clinical studies show elevated cytokine levels in patients with chronic pain conditions such as back pain,[27] post-herpetic neuralgia,[28] and unstable angina.[29,30] In animal studies, IL8 has been found to evoke a dose dependent hyperalgesia.[31] Studies have also suggested that IL6 and TNF-α cause hyperexcitability in pain transmission neurons and the exaggerated release of substance P and excitatory amino acids from presynaptic terminals produces an exaggerated pain response. [29,32]

Because inflammatory cytokines have been associated with pain, depression, fatigue and QOL impairments,[33] there may be shared biological mechanisms for these symptoms. It is also possible that there may be a polygeneic model for pain, with other cytokines and biological mechanisms involved in the modulation of nociceptive input. However, it remains unclear whether these pathways are associated with pain and QOL in long term lung cancer survivors.

Inflammatory Pathway Genes

Recently, greater empirical attention has focused on the identification of genetic polymorphisms of inflammatory markers among cancer patients. Single nucleotide polymorphisms (SNPs) have been linked not only to increased susceptibility of cancer [34–38] and survival [39–41] but more recently to cancer outcomes, such as cachexia,[42,43] pain,[29,33], fatigue,[20,33] appetite, [33] dyspnea, [33] fibrosis, [44–46] and QOL.[33]

Prostaglandin-endoperoxide synthase 2 (PTGS2) encodes the cyclooxygenase 2 (COX2) enzyme, is pivotal in the production of prostaglandins, and plays a role in inflammation and pain.[47] The role of prostaglandins is particularly important in cancer patients, as cancer cells and their macrophages produce prostaglandins, which have been shown to sensitize or excite pain receptors.[48–49] PTGS2 SNPs have been associated with risk of bladder cancer,[50] basal cell carcinoma,[51] survival in colorectal cancer,[52] risk of gallbladder cancer, [53] risk of ovarian cancer,[54] acute coronary syndrome,[55]and acute pancreatitis. [56]

One PTGS2 SNP, Rs5277, has been associated with risk of breast cancer,[57] acute pancreatitis, [56] and risk for colorectal adenoma. [58] To our knowledge, only one study has examined the association between PTGS2 SNPs and pain among cancer patients. Reyes-Gibby and colleagues found an association between PTGS2 SNPs (rs5275) and pain severity among a sample of 667 newly diagnosed lung cancer patients.[49]

Another important inflammatory marker, lymphotoxin-alpha (LTA/TNF-β), a member of the Tumor Necrosis Factor (TNF) family of inflammatory cytokines, also plays a significant role in inflammation.[59–61]. TNF-alpha has been found to be a central member of the cytokine mediator system that is intrinsic to the pathogenesis of pain at both the peripheral and central levels.[18] Although the potential link between LTA SNPs and cancer pain has yet to be examined, the existence of a link between TNF-α and cancer pain,[62–64] and the similarity between TNF-α and LTA argue for the investigation of this potential link. To date, the only published report found in a literature search examining an association with the LTA SNP evaluated herein, Rs1799964, found it was associated with an increased incidence of Grave's disease.

The Importance of Examining SNPs

Due to the large body of literature suggesting links between serum cytokine levels with cancer symptoms, our previous work examined the relationship of cytokine SNPs, QOL, and symptom burden in long term lung cancer survivors. [33] We found significant associations between cytokine SNPs and lung cancer QOL and symptom burden, mirroring the reported relationships observed with levels of serum cytokines. Therefore, based on our previous work, we further examined SNPs of other genetic markers of inflammation (i.e., LTA, PTGS2) that we anticipated would play a primary role in cancer pain for long term lung cancer survivors.

Identification of the underlying causes of symptom evolution would be beneficial for controlling disease-related and treatment-related late and long-term effects. This includes identification of possible biological mechanisms such as inflammation, that may account for the generation and sustenance of symptoms, and development of biological interventions that ameliorate those processes.

METHODS

Research Design and Methods

Participants—All participants for this study were enrolled in the Epidemiology and Genetics of Lung Cancer Research Program at Mayo Clinic Rochester (Mayo Clinic Lung Cancer Cohort; MCLCC [65]). Since January 1, 1997, all patients at our institution who were diagnosed with lung cancer have been offered participation in this prospective cohort study. Participation rate has been over 90% of eligible lung cancer patients.[65,66] All patients provided written informed consent and the study has been approved by the Mayo Clinic IRB on an annual basis. Upon enrollment, all patients complete baseline health-related surveys and are then mailed similar surveys on an annual basis. The follow-up process started within six months after diagnosis and then annually until patients' death.

Information on demographics, previous or concurrent illnesses, tobacco usage and exposure, tumor staging, and cancer therapy were abstracted by study personnel from medical records and entered into the database. Participants self-identified their race on questionnaires. We have also obtained comprehensive data from patients beyond the ordinary demographic and clinical information at the time of diagnosis. These data were collected through patient interviews and periodic follow-up. For example, ethnicity background was obtained based on self-reported country-of-origin of a patient's four grandparents.[65] Specifics on ongoing patient recruitment, baseline data retrieval, and patient follow-up are described in the larger MCLCC studies.[65]

Genotyping Methods

All SNP analyses were conducted using the Illumina GoldenGate Genotyping Assay (a flexible, pre-optimized assay that uses a discriminatory DNA polymerase and ligase to interrogate up to 1500 SNP loci simultaneously). Because of the established relationship between serum cytokines and psychosocial variables, COX and pain, and our previous work in cytokine SNPs and lung cancer, the LTA and PTGS2 genes were chosen to evaluate the relationship between these inflammatory marker SNPs and lung cancer symptoms and QOL variables. SNP selection involved identifying tag SNPs for the genes. To accomplish this, genotype data from the HapMap consortium, Seattle SNPs, Perlegen Sciences, and Panel 2 of the National Institute for Environmental Health Sciences were analyzed with ldSelect to bin SNPs with European American MAF >0.05 at a pairwise linkage disequilibrium (LD) threshold of $r^2 \geq 0.8$. The region for each gene included 5kb upstream and downstream. See Table 1 for the ten selected PTGS2 and LTA SNPs.

Tag-SNPs on these genes were selected based on HapMap data (Release 22/Phase II on NCBI B36) by Haploview, Version 3, using the Caucasian (CEU) data available from HapMap. Tag-SNP selection parameters ignored pairwise comparisons of markers greater than 500 kb apart; excluded individuals with greater than 50% missing genotypes; excluded SNPs with Hardy-Weinberg *p*-values of less than 0.001, SNPs with fewer than 75% genotype calls, SNPs with more than one Mendelian error, and SNPs with a minor allele frequency less than 0.001; performed aggressive tagging using a r^2 threshold of 0.8, and included a LOD threshold for multi-marker tests of three.

Genotyping was performed in the Mayo Clinic Genomic Shared Resource following the manufacturer's protocol. The concentration of all DNA samples was verified using pico green. For quality control a CEPH DNA trio (parents and child, Coriell Institute), each in duplicate, and two sample replicates were included in each 96-well plate. Resultant data were generated and transferred electronically to a secure server or ftp drop site. The average sample call rate was 99.5%.

Self-reported QOL

Medical Outcomes Study Short-Form General Health Survey (SF-8; [67])—The SF-8 is a brief version of the SF-36 and contains 8 items yielding 8 separate subscales of health related QOL: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. The SF-36 and the SF-8

have been widely used in cancer health-related QOL studies and have been shown to have high reliability and validity when utilized in cancer populations.[68–71]

RESULTS

Preliminary Analyses

Demographic and Disease Data—A total of 1149 Caucasian lung cancer patients in the Mayo Clinic Lung Cancer Epidemiology Project had both self-report and genetic data. See Table 2 for demographic and disease variables for the 1149 patients in our analyses.

Mean Scores and Change across time periods—Results were divided by the time in which the lung cancer survivor last completed questionnaires after receiving their diagnosis. Due to our relatively large sample, we were able to divide our results into three groups, based on the years of survivorship: early survivors defined as <3 years, middle term survivors defined as 3–5 years, and long term survivors defined as >5 years since lung cancer diagnosis. Thus, we were able to capture the full spectrum of possible survivorship time classifications.

All items on the SF-8 were negatively valenced with higher scores representing poor outcomes (e.g. worst pain imaginable, worst possible QOL). Therefore higher numbers represent worse outcomes on all measures. See Table 3 for SF-8 means in the participants.

The SNPs were coded as categorical variables with three levels (0, 1, 2), indicating the number of minor allele (see Table 4). Any SNP with minor allele frequency less than 5% was excluded from the analysis; some SNPs had either lever 1 or level 2 less than 5%, and these two levels were be combined. The average QOL domain scores were compared across different levels using a single two-sample independent samples *t*-test or Wilcoxon rank sum test as appropriate for each time period.

Preliminary analyses evaluated the relationship between pain and QOL outcomes. Spearman coefficient and multivariate linear regression modeling of SF-8 bodily pain were used to explore the relationship between pain and QOL within SF-8 items. The covariates considered in the models were: age at diagnosis, gender, smoking status and disease stage. Table 5 shows the inter-item correlation between SF-8 bodily pain and QOL. Table 6 shows the Results of multivariate linear regression model between SF-8 bodily pain and QOL, adjusted for patient baseline characteristics.

The primary analyses were based on conditional logistic regression modeling of SNP level after collinearity diagnostics to ascertain the independence and contribution of the covariates. The covariates considered in the models were: age at diagnosis, gender, smoking status, disease stage, and treatment modality. The methods of Belsey [72] were applied to assess the degree of collinearity before modeling processes were initiated. Specifically, Belsey recommends the use of a variance inflation factor (VIF) statistic and condition index (CI) to assess multicollinearity and provides guidelines and thresholds for acceptable levels of collinearity (VIF below 5 and CI below 30).

A multivariable conditional stepwise logistic regression method with the likelihood ratio criterion (inclusion/exclusion criteria: $P < 0.15/P > 0.15$, respectively) was used to investigate the relationship between the SNP and SF-8 variables for each time period. This approach was used to develop predictive models adjusting for other potential risk factors identified from the previous analyses such as age at diagnosis, gender, smoking status, disease stage, and treatment modality. Bonferroni's correction was utilized to account for the multiple analyses. Criteria for reaching clinical significance was defined by having at least a 1 standard deviation difference in mean score on outcomes, compared to the other allele frequencies. Table 7 shows the statistically significant findings *after* Bonferroni's correction, *and* clinical significance.

Using the conditional logistic multiple regression modeling, we found four significant relationships between three of the ten SNPs and SF-8 outcomes. Specifically, in 3–5 year survivors, SNPs in PTGS2 were associated with pain (rs5277), social function (rs5277) and mental health (rs5275). In 5+ year survivors, a SNP in LTA (rs1799964) was associated with pain. In the PTGS2 SNPS: For rs5277, people carrying one or two minor (G) alleles reported higher scores for pain and lower scores for social function. For rs5275, people carrying one or two minor (G) alleles reported lower scores for mental health. In the LTA SNP: For rs1799964, people carrying one or two minor (G) alleles reported lower pain scores.

DISCUSSION

Pain and diminished QOL are prevalent problems for cancer survivors. Effective identification of patients at risk for uncontrolled cancer pain could significantly reduce cancer burden and improve the QOL for cancer survivors. We found pain and QOL to be moderately correlated, and pain accounted for a significant portion of the variance in the QOL domains, above and beyond patient baseline characteristics.

Several studies have suggested genetic markers for cancer survivorship. However, only recently has research begun to investigate the potential effects of gene polymorphisms on pain and QOL among cancer survivors, and ours was the first to our knowledge in long term cancer survivors. Unfortunately, the studies conducted have often had small sample sizes, and/or only included short term survivors. This study successfully recruited a large cohort of long term lung cancer survivors and found statistically significant and clinically meaningful associations between SNPs and pain and QOL variables (mental health and social function), while controlling for important demographic and clinical variables related to cancer treatment outcomes.

Because SNPs are stable biomarkers that are not affected by tumor or medical treatment, we believe that these findings represent a potential predictive model for the identification of individuals at high risk for cancer pain and associated poor QOL. These findings are consistent with a previous study [49] reporting a PTGS2 SNP (rs5275) being associated with pain severity in newly diagnosed lung cancer patients. Therefore, the findings from this study provide further support for the foundation of a predictive model for cancer pain. Interestingly, we did not find any associations in the early survivors (<3 years), providing

more rationale for conducting studies with different groups of survivors by length of survivorship. Our data, and previous studies have shown different levels of symptom burden and QOL outcomes by length of survivorship.[5,73]

Considering that the pain-related healthcare costs of cancer patients with breakthrough pain are five times greater than those for cancer patients without breakthrough pain,[74] early identification and effective personalized treatment of patients at elevated risk for cancer pain could also provide financial benefit as well as improved patient QOL.

If future research can confirm these findings, gene SNPs have the potential be used to identify cancer survivors at elevated risk for a variety of symptoms, including uncontrolled pain and poor QOL. Indeed, genetic polymorphisms have been linked to several cancer symptoms, including QOL.[33] In concert with heightened surveillance and tailored treatments, these findings could potentially be used to significantly reduce suffering in cancer survivors by guiding early identification and intervention of troubling symptoms such as pain and poor QOL.

In addition to worse pain, the same SNP (rs5277) was found to be significantly associated with worse social function, and a similar SNP (rs5275) to be associated with mental health. Given the apparent specificity of this gene for pain mechanisms, and the close interrelations among pain and QOL, it is our premise that this finding is a result of the impact of the pain pathway on the cancer survivors' social and mental functioning. Pain certainly impacts QOL[75] as pain has been shown to impact various domains of QOL including physical function, role function, role limitations, social functioning, and general health perceptions among cancer patients.[13,76,77] In fact, reports indicate that up to 53% of the variance in QOL has been accounted for by symptom burden from pain and mood.[13] QOL has been directly related to pain severity, pain interference, pain relief, and pain management in mixed cancer [75] and lung cancer [78] populations.

In our previous work,[33] we found mental health to be related to IL-1 SNPs and social function to IL-6, IL-1, and TNF-a SNPs, all pro-inflammatory cytokine pathways. Therefore, it is certainly plausible that a dysregulated inflammatory response may be implicated with these domains of QOL. However with the specificity of our findings with pain (only specific SNPS) and the correlation between pain and QOL, we presume that these findings are related to the impact of pain on these QOL domains. However, replication and extension of these findings are needed before definitive conclusions can be drawn regarding the temporal relationships of these associations.

The ultimate goal of symptom-based research in survivors is to prevent debilitating long-term and late effects from ever developing, and if they do, to be able to treat them effectively. To further this goal, researchers must study factors, which could include genetic markers that may put an individual at high risk for certain symptoms. Identification of biological mechanisms such as inflammatory processes would be essential in a comprehensive understanding to early identification of those at high risk, and effectively treating symptoms.

Strengths & Limitations

To our knowledge, our study is among the first to examine the relationships between genetic polymorphisms and pain and quality of life variables, and has several advantages over previous studies. First, our study's large sample (n = 1,149) allowed the examination of several SNPs for both genes studied. Additionally we were able to evaluate separately, groups of different cancer survivor classifications (<3 years, 3–5 years, >5 years) as they may be clinically very different populations. Our results suggested this association was both clinically meaningful, and statistically significant. In addition, because recent studies have suggested a link between smoking status and pain among cancer patients,[64,65] we feel the inclusion of smoking status, along with all other demographic and disease variables as a covariate in this study was a strength of the study.

Limitations of this study include the lack of a control group and the homogeneity of the sample. Thus, this study's findings are only generalizable to Caucasian lung cancer survivors. Also, although this was not assessed, it is possible that the lung cancer survivors who declined to participate in the study, as well as those participants who failed to complete some study measures were experiencing more severe declines in their health status. Those in critical health condition may not have been physically able or psychologically motivated to complete the study measures. Although the focus of our study and this paper is on cancer-related pain, the SF-8 bodily pain question does not specifically ask respondents to only report their cancer-related pain. Therefore, it is possible that patients may have pain that is not related to cancer. Lastly, because analgesic use was not assessed, we were unable to include analgesic use as a covariate in multivariate analyses.

CONCLUSION

In conclusion, previous research has documented that lung cancer patients suffer from the lowest QOL of all cancer survivors, and high rates of pain.[3] Breakthrough pain among cancer patients is associated with lower QOL, greater symptom burden and healthcare costs. This study found three SNPs for PTGS2 and LTA inflammatory markers were associated with pain and QOL in a large sample of long term lung cancer survivors. We believe that the two QOL domain (mental health and social function) findings were related to pain, as pain was significantly associated with QOL. Replication and extension of these findings could yield beneficial information regarding which cancer survivors are at increased risk of pain, which could guide treatment decisions and potentially improve the QOL of long term lung cancer survivors. Late and long-term effects seen in cancer survivors have historically been understudied. Symptom burden is an important area of assessment that can be used to specifically describe distress in survivors. Biological processes related to this distress may aid in identifying symptom production and maintenance and facilitate in the development of better treatment and prevention to enhance survivorship.

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Table 1

Ten SNPs selected

PTGS2 SNPs	LTA SNPs
rs2206593	rs1041981
rs2745557	rs2071590
rs4648261	rs1799964
rs4648307	rs3093542
rs5275	
rs5277	

Table 2

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

Age at Diagnosis	
Mean (SD)	65.2 (9.47)
Median	66.0
Range	(35.0–89.0)
Gender	
Female	540 (47%)
Male	609 (53%)
Race	
Caucasian	1149 (100%)
Pathologic Cell type	
ADENOCARCINOMA	525 (45.7%)
SQUAMOUS	260 (22.6%)
SMALL CELL	146 (12.7%)
NON-SMALL CELL	60 (5.2%)
OTHER	157 (13.7%)
MISSING	1 (0.01%)
Stage	
Unknown	8 (0.01%)
STAGE I	584 (51.2 %)
STAGE II	110 (9.6%)
STAGE III	234 (19.6%)
STAGE IV	223 (20.5%)
Cigarette smoking status	
Never	194 (16.9%)
Former	580 (50.5%)
Current	369 (32.1%)
Missing	6 (0.5%)

Table 3

Mean Scores for Each Variable by Length of Survivorship

	Survivorship Classification		
SF-8 Domain:	**<3yrs *n*=440**	**3–5yrs *n*=354**	**>5yrs *n*=355**
General Health	44.32	45.01	45.98
Physical Function	38.72	40.08	40.16
Role Physical	38.35	40.36	40.92
Bodily Pain	48.21	48.91	49.73
Vitality	44.56	47.34	48.09
Social Function	42.70	44.76	45.29
Mental Health	47.27	48.91	48.94
Role Emotional	43.45	45.75	45.42
Physical Component	39.59	41.26	42.02
Mental Component	47.46	49.97	49.99

Table 4

Number of minor alleles for each SNP

SNP	Minor Allele Count			
	0 (no minor allele)	1 (one copy of the minor allele or heterozygote)	2 (two copies of the minor alleles or homozygote)	Missing
LTA	**N(%)**	**N(%)**	**N(%)**	**N**
•rs1041981	561 (43%)	550 (42%)	195 (15%)	13
•rs2071590	538 (42%)	426 (34%)	310 (24%)	45
•rs1799964	832 (63%)	417 (32%)	69 (5%)	1
•rs3093542	1234 (93%)	84 (6%)	1 (1%)	0
PTGS2	**N(%)**	**N(%)**	**N(%)**	**N**
•rs4648307	1032 (78%)	265 (20%)	22 (6%)	0
•rs2745557	883 (67%)	386 (29%)	48 (4%)	2
•rs5277	930 (71%)	345 (26%)	44 (3%)	0
•rs2206593	1172 (89%)	136 (10%)	9 (1%)	2
•rs5275	610 (46%)	559 (43%)	150 (11%)	0
•rs4648261	1233 (93%)	84 (6%)	1 (1%)	1

Table 5

Inter-item correlation between SF-8 bodily pain and other SF-8 components

Survivorship Classification	General Health	Physical Function	Role Physical	Vitality	Social Function	Mental Health	Role Emotion	Physical Component	Mental Component
<3yrs	0.43	0.37	0.37	0.39	0.36	0.31	0.22	0.62	0.30
3–5yrs	0.55	0.50	0.55	0.43	0.49	0.34	0.35	0.72	0.33
>5yrs	0.49	0.48	0.49	0.43	0.51	0.43	0.49	0.69	0.44

Table 6

Results of multivariate linear regression model between SF-8 pain and QOL, adjusted for patient baseline characteristics.

QOL Domain	Survivorship Classification					
	<3yrs		3–5yrs		>5yrs	
	β	P value	β	P value	β	P value
General Health	−0.54	<.0001	−0.57	<.0001	−0.56	<.0001
Physical Function	−1.05	<.0001	−0.95	<.0001	−0.98	<.0001
Role Physical	−1.57	<.0001	−1.50	<.0001	−1.51	<.0001
Vitality	−0.07	0.3213	−0.22	<.0001	−0.18	<.0001
Social Function	0.15	0.0132	0.03	0.4715	0.06	0.0943
Mental Health	1.50	<.0001	1.08	<.0001	1.17	<.0001
Role Emotion	0.23	0.0297	0.02	0.8035	0.07	0.2676
Physical Component	2.88	<.0001	2.92	<.0001	2.91	<.0001
Mental Component	−0.88	0.0020	−0.32	0.1106	−0.44	0.0048

Table 7

Significant Associations between SNPs and QOL Domains (SF-8)

SF-8 Domain	Period	Cytokine	SNP	Minor Allele	Odds Ratio Estimate*
Bodily Pain	2	PTGS2	rs5277	G	1.02–1.11
	3	LTA	rs1799964	G	0.92–0.98
Mental Health	2	PTGS2	rs5275	G	0.89–0.99
Social Function	2	PTGS2	rs5277	G	0.90–0.98

*95% confidence interval of the odds ratio estimate