Lung Cancer 77 (2012) 217–223

Contents lists available at SciVerse ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

SNPs in PTGS2 and LTA predict pain and quality of life in long term lung cancer survivors

Sarah M. Rausch[a,*], Brian D. Gonzalez[a], Matthew M. Clark[b], Christi Patten[b], Sara Felten[b], Heshan Liu[b], Yafei Li[b], Jeff Sloan[b], Ping Yang[b]

[a] Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, Tampa, FL 33612, United States
[b] Mayo Clinic, 200 First St SW, Rochester, MN 55905, United States

ARTICLE INFO

Article history:
Received 15 June 2011
Received in revised form 18 January 2012
Accepted 22 February 2012

Keywords:
Genetics
SNPs
Pain
Quality of life
Lung cancer
Cytokines
LTA
PTGS2

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 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 blood DNA samples available. Ten SNPS from PTGS2 and LTA genes were selected based on the serum-based studies in the 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 lung cancer survivors.
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.

1. Introduction

1.1. 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,

* Corresponding author. Tel.: +1 813 745 2194; fax: +1 813 745 3906.
E-mail addresses: sarah.rausch@moffitt.org (S.M. Rausch), Brian.gonzalez@moffitt.org (B.D. Gonzalez), Clark.matthew@mayo.edu (M.M. Clark), Patten.christi@mayo.edu (C. Patten), Felten.sara@mayo.edu (S. Felten), Liu.heshan@mayo.edu (H. Liu), li.yafei@mayo.edu (Y. Li), Sloan.jeff@mayo.edu (J. Sloan), Yang.ping@mayo.edu (P. Yang).

0169-5002/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2012.02.017

impingement of tumor on adjacent tissue, obstruction of blood vessels, chemotherapeutic agents, damage to the 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.

1.2. 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 the activity of nociceptors contributing to pain hypersensitivity. Clinical studies show elevated cytokine levels in patients with chronic pain conditions such as back pain [27], postherpetic 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.

1.3. 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 et al. 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.

1.4. 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.

2. Methods

2.1. Research design and methods

2.1.1. 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 [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

Table 1
Ten SNPs selected.

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

health-related surveys. 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].

2.1.2. 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 5 kb 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 an 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%.

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%)

2.2. Self-reported QOL

2.2.1. 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].

3. Results

3.1. 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

Table 3
Mean scores for each variable by length of survivorship.

SF-8 domain	Survivorship classification		
	<3 years *N* = 440	3–5 years *N* = 354	>5 years *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

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.

4. 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

Table 4
Number of minor alleles for each SNP.

SNP	Minor allele count			
	0 (no minor allele) *N* (%)	1 (one copy of the minor allele or heterozygote) *N* (%)	2 (two copies of the minor alleles or homozygote) *N* (%)	Missing *N*
LTA				
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				
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
<3 years	0.43	0.37	0.37	0.39	0.36	0.31	0.22	0.62	0.30
3–5 years	0.55	0.50	0.55	0.43	0.49	0.34	0.35	0.72	0.33
>5 years	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					
	<3 years		3–5 years		>5 years	
	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

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.

4.1. Strengths and 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 ($N = 1149$) 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

Table 7
Significant associations between SNPs and QOL domains (SF-8).

SF-8 domain	Survivorship Classification	Cytokine	SNP	Minor allele	Odds ratio estimate[a]
Bodily Pain	3–5 years	PTGS2	rs5277	G	1.02–1.11
	>5 years	LTA	rs1799964	G	0.92–0.98
Mental Health	3–5 years	PTGS2	rs5275	G	0.89–0.99
Social Function	3–5 years	PTGS2	rs5277	G	0.90–0.98

[a] 95% confidence interval of the odds ratio estimate.

addition, because recent studies have suggested a link between smoking status and pain among cancer patients [64,65], we feel that 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.

5. 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 that 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.

Conflict of interest statement

None to declare.

Acknowledgment

This research was funded in part by the National Cancer Institute, grant numbers 5R01CA115857 and 5R01CA084354 (Yang, P.I.).

References

[1] Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors 2001: systematic analysis of population health data. Lancet 2006;367(Suppl. 9524):1747–57.
[2] Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, et al., editors. SEER cancer statistics review, 1975–2008. Bethesda, MD: National Cancer Institute; 2011. http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site.
[3] Sugimara H, Yang P. Long-term survivorship in lung cancer: a review. Chest 2006;129(4):1088–97.
[4] Burkett VS, Cleeland CS. Symptom burden in cancer Survivorship. J Cancer Surviv 2007;1:167–75.
[5] Yang P, Cheville AL, Wampfler JA, Garces YI, Jatoi A, Clark MM, et al. Quality of life and symptom burden among long-term lung cancer survivors. J Thorac Oncol 2012;7(January (1)):64–70.
[6] Balduyck B, Hendriks J, Lauwers P, Van Schil P. Quality of life after lung cancer surgery. J Thorac Oncol 2008;3(June (6)):604–8.
[7] Mantyh PW. Cancer pain and its impact on diagnosis, survival and quality of life. Nat Rev Neurosci 2006;7(October (10)):797–809.
[8] Patrick DL, Ferketich SL, Frame PS, Harris JJ, Hendricks CB, Levin B, et al. National Institutes of Health State-of-the-Science conference statement: symptom management in cancer: pain, depression, and fatigue, July 15–17, 2002. J Natl Cancer Inst Monogr 2004;32:9–16.
[9] Grossman SA, Sheidler CR. Cancer pain. In: Aeloff MD, Armitage JO, Lichter AS, et al., editors. Clinical oncology. 2nd ed. New York (NY): Churchill Livingstone; 2000. p. 565–78.
[10] Wang XS, Cleeland CS, Mendoza TR, Engstrom MC, Liu S, Xu G, et al. The effects of pain severity on health-related quality of life. Cancer 1999;86(Suppl. 9):1848–55.
[11] de Wit R, van Dam F, Loonstra S, Zandbelt L, van Buuren A, van der Heidjen K, et al. The Amsterdam Pain Management Index compared to eight frequently used outcome measures to evaluate the adequacy of pain treatment in cancer patients with chronic pain. Pain 2001;91(Suppl. 3):339–49.
[12] Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA, Grond S. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. Pain 2001;93(Suppl. 3):247–57.
[13] Cheng KKF, Lee DTF. Effects of pain, fatigue, insomnia, and mood disturbance on functional status and quality of life of elderly patients with cancer. Crit Rev Oncol Hematol 2010.
[14] Strömgren AS, Sjogren P, Goldschmidt D, Petersen MA, Pederson L, Groenvold M. Symptom priority and course of symptomatology in specialized palliative care. J Pain Symptom Manage 2006;31(Suppl. 3):199–206.
[15] Green CR, Hart-Johnson T, Loeffleer DR. Cancer-related chronic pain: examining quality of life in diverse cancer survivors. Cancer 2011:1994–2003.
[16] Davis K, Yount S, Wagner L, Cella D. Measurement and management of health-related quality f life in lung cancer. Clin Adv Hematol Oncol 2004;2(8):533–40.
[17] Burton AW, Fanciullo GJ, Beasley RD, Fisch MJ. Chronic pain in the cancer survivor: a new frontier. Pain Med 2007;8(2):189–98.
[18] Leung L, Cahill CM. TNF-alpha and neuropathic pain – a review. J Neuroinflamm 2010;7:27–38.
[19] Seruga B, Zhang H, Bernstein LJ, Tannock IF. Cytokines and their relationship to the symptoms and outcome of cancer. Nature 2008;8(Suppl. 11):887–99.
[20] Collado-Hidalgo A, Bower JE, Ganz PA, Cole SW, Irwin MR. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. Clin Cancer Res 2006;12(Suppl. 9):2759–66.
[21] O'Connor MF, Irwin MR, Seldon J, Kwan L, Ganz PA. Pro-inflammatory cytokines and depression in a familial cancer registry. Psychooncology 2007;16(Suppl. 5):499–501.
[22] Musselman DL, Miller AH, Porter MR, Manatunga A, Gao F, Penna S, et al. Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings. Am J Psychiatry 2001;158(Suppl. 8):1252–7.
[23] Jehn CF, Kuhnhardt D, Bartholomae A, Pfeiffer S, Schmid P, Possinger K, et al. Association of IL-6. Hypothalamus-pituitary-adrenal axis function, and depression in patients with cancer. Integr Cancer Ther 2010;9(3):270–5.
[24] Wang XS, Shi Q, Williams LA, Mao L, Cleeland CS, Komaki RR, et al. Inflammatory cytokines are associated with the development of symptom burden in patients with NSCLC undergoing concurrent chemoradiation therapy. Brain Behav Immun 2010;24:968–74.
[25] Panju AH, Danesh A, Minden MD, Kelvin DJ, Alibhai SM. Associations between quality of life, fatigue, and cytokine levels in patients aged 50 with acute myeloid leukemia. Support Care Cancer 2009;17(Suppl. 5):539–46.
[26] Del Fabbro E, Hui D, Nooruddin Z, Dalal S, Dev R, Freer G, et al. Association between inflammatory markers, symptom burden, hypogonadism, and survival in cancer patients with cachexia. J Clin Oncol 2009;27(Suppl. 15S):9594.
[27] Brisby H, Olmarker K, Larsson K, Nutu M, Rydevik B. Proinflammatory cytokines in cerebrospinal fluid and serum in patients with disc herniation and sciatica. Eur Spine J 2002;11:62–6.
[28] Kotani N, Kudo R, Sakurai Y, Sawamura D, Sessler DI, Okada H, et al. Cerebrospinal fluid interleukin 8 concentrations and the subsequent development of posttherapeutic neuralgia. Am J Med 2004;116:318–24.
[29] Reyes-Gibby CC, Spitz M, Wu X, Merriman K, Etzel C, Bruera E, et al. Cytokine genes and pain severity in lung cancer: exploring the influence of TNF-α-308 G/A IL6-174G/C and IL8-251T/A. Cancer Epidemiol Biomarkers Prev 2007;16(Suppl. 12):2745–51.
[30] Zhou RH, Shi Q, Gao HQ, Shen BJ. Changes in serum interleukin-8 and interleukin-12 levels in patients with ischemic heart disease in a Chinese population. J Atheroscler Thromb 2001;8:30–2.
[31] Cunha FQ, Lorenzetti BB, Poole S, Ferreira SH. Interleukin-8 as a mediator of sympathetic pain. Br J Pharmacol 1991;104:765–7.
[32] Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychol Rev 1998;105:83–107.
[33] Rausch SM, Clark MM, Patten C, Liu H, Felten S, Li Y, et al. Relationship between cytokine gene single nucleotide polymorphisms and symptom burden and quality of life in lung cancer survivors. Cancer 2010;116(Suppl. 7):4103–13.
[34] Chouchane L, Ahmed SB, Baccouche S, Remadi S. Polymorphism in the tumor necrosis factor-α promoter region and in the heat shock protein

70 genes associated with malignant tumors. Cancer 1997;80(Suppl. 8): 1489–96.
[35] Howell WM, Rose-Zerilli MJ. Cytokine gene polymorphisms, cancer susceptibility, and prognosis. J Nutr 2007;137(Suppl. 1):194S–9S.
[36] Rothman N, Skibola CF, Wang SS, Morgan G, Lan Q, Smith MT, et al. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. Lancet Oncol 2006;7(Suppl. 1):27–38.
[37] Sasaki M, Tanaka Y, Kaneuchi M, Sakuragi N, Dahiya R. Polymorphisms of estrogen receptor [alpha] gene in endometrial cancer. Biochem Biophys Res Commun 2002;297(Suppl. 3):558–64.
[38] Shi Q, Zhang Z, Li G, Pillow PC, Hernandez LM, Spitz MR. Sex differences in risk of lung cancer associated with methylene-tetrahydrofolate reductase polymorphisms. Cancer Epidemiol Biomarkers Prev 2005;14(Suppl. 6):1477–84.
[39] Lech-Maranda E, Baseggio L, Bienvenu J, Charlot C, Berger F, Rigal D. Interleukin-10 gene promoter polymorphisms influence the clinical outcome of diffuse large B-cell lymphoma. Blood 2004;103(Suppl. 9):3529–34.
[40] Lee JM, Wu MT, Lee YC, Yang SY, Chen JS, Hsu HH, et al. Association of GSTP1 polymorphism and survival for esophageal cancer. Clin Cancer Res 2005;11(Suppl. 13):4749–53.
[41] Vuoristo MS. The polymorphisms of interleukin-10 gene influence the prognosis of patients with advanced melanoma. Cancer Genet Cytogenet 2007;176(Suppl. 1):54–7.
[42] Jatoi A, Nguyen PL, Foster N, Sun D, Stella PJ, Campbell M, et al. Interleukin-1 genetic polymorphisms and their relationship to the cancer anorexia/weight loss syndrome in metastatic gastric and gastroesophageal junction adenocarcinoma. J Support Oncol 2007;5(Suppl. 1):41–6.
[43] Zhang D, Zhou Y, Wu L, Wang S, Zheng H, Yu B, et al. Association of IL-6 gene polymorphisms with cachexia susceptibility and survival time of patients with pancreatic cancer. Ann Clin Lab Sci 2008;38(Suppl. 2):113–9.
[44] Andreassen CN, Overgaard J, Alsner J, Overgaard M, Herskind C, Cesaretti JA, et al. ATM sequence variants and risk of radiation-induced subcutaneous fibrosis after postmastectomy radiotherapy. Int J Radiat Oncol Biol Phys 2006;64(Suppl. 3):776–83.
[45] De Ruyck K, Van Eijkeren M, Claes K, Mothier R, De Paepe A, Vral A, et al. Radiation-induced damage to normal tissues after radiotherapy in patients treated for gynecologic tumors: association with single nucleotide polymorphisms in XRCC1, XRCC3, and OGG1 genes and in vitro chromosomal radiosensitivity in lymphocytes. Intl J Radiat Oncol Biol Phys 2005;62(Suppl. 4):1140–9.
[46] Quarmby S, Fakhoury H, Levine E, Barber J, Wylie J, Hajeer AH, et al. Association of transforming growth factor beta-1 single nucleotide polymorphisms with radiation-induced damage to normal tissues in breast cancer patients. Int J Radiat Biol 2003;79(Suppl. 2):137–43.
[47] Hussain T, Gupta S, Mukhtar H. Cyclooxygenase-2 and prostate carcinogenesis. Cancer Lett 2003;191(Suppl. 2):125–35.
[48] Mantyh PW, Clohisy DR, Koltzenburg M, Hunt SP. Molecular mechanisms of cancer pain. Nat Rev Cancer 2002;2(Suppl. 3):201–9.
[49] Reyes-Gibby CC, Spitz MR, Yennurajalingam S, Swartz M, Gu J, Wu X, et al. Role of inflammation gene polymorphisms on pain severity in lung cancer patients. Cancer Epidemiol Biomarkers Prev 2009;18(Suppl. 10):2636–42.
[50] Yang H, Gu J, Lin X, Grossman HB, Ye Y, Dinney CP, et al. Profiling of genetic variations in inflammation pathway genes in relation to bladder cancer predisposition. Clin Cancer Res 2008;14(Suppl. 7):2236–44.
[51] Vogel U, Christensen J, Wallin H, Friis S, Nexo BA, Tjonneland A. Polymorphisms in COX-2, NSAID use and risk of basal cell carcinoma in a prospective study of Danes. Mutat Res 2007;617(Suppl. 1–2):138–46.
[52] Kim JG, Chae YS, Sohn SK, Moon JH, Ryoo HM, Bae SH, et al. Prostaglandin synthase 2/cyclooxygenase 2 (PTGS2/COX2) 8473T>C polymorphism associated with prognosis for patients with colorectal cancer treated with capecitabine and oxaliplatin. Cancer Chemother Pharmacol 2009;64(Suppl. 5):953–60.
[53] Srivastava K, Srivastava A, Pandey SN, Kumar A, Mittal B. Functional polymorphisms of the cyclooxygenase (PTGS2) gene and risk for gallbladder cancer in a North Indian population. J Gastroenterol 2009;44(Suppl. 7):774–80.
[54] Lurie G, Terry KL, Wilkens LR, Thompson PJ, McDuffie KE, Carney ME, et al. Pooled analysis of the association of PTGS2 rs5275 polymorphism and NSAID use with invasive ovarian carcinoma risk. Cancer Causes Control 2010;21(Suppl. 10):1731–41.
[55] Vogel U, Segel S, Dethlefsen C, Tjonneland A, Saber AT, Wallin H, et al. Associations between COX-2 polymorphisms, blood cholesterol and risk of acute coronary syndrome. Atherosclerosis 2010;209(Suppl. 1):155–62.
[56] Ozhan G, Yanar TH, Ertekin C, Alpertunga B. The effect of genetic polymorphisms of cyclooxygenase 2 on acute pancreatitis in Turkey. Pancreas 2010;39(Suppl. 3):371–6.
[57] Yu KD, Chen AX, Yang C, Qiu LX, Fan L, Xu WH, et al. Current evidence on the relationship between polymorphisms in the COX-2 gene and breast cancer risk: a meta-analysis. Breast Cancer Res Treat 2010;122(Suppl. 1):251–7.
[58] Barry EL, Sansbury LB, Grau MV, Ali IU, Tsang S, Munroe DJ, et al. Cyclooxygenase-2 Polymorphisms, aspirin treatment, and risk for colorectal adenoma recurrence—data from a randomized clinical trial. Cancer Epidemiol Biomarkers Prev 2009;18(Suppl. 10):2726.
[59] Cuff CA, Sacca R, Ruddle NH. Differential induction of adhesion molecule and chemokine expression by LT α3 and LTαβ in inflammation elucidates potential mechanisms of mesenteric and peripheral lymph node development. J Immunol 1999;162(Suppl. 10):5965–72.
[60] Hjelmstrom P, Fjell J, Nakagawa T, Sacca R, Cuff CA, Ruddle NH. Lymphoid tissue homing chemokines are expressed in chronic inflammation. Am J Pathol 2000;156(Suppl. 4):1133–8.
[61] Sacca R, Cuff CA, Lesslauer W, Ruddle NH. Differential activities of secreted lymphotoxin-α3 and membrane lymphotoxin-α1β2 in lymphotoxin-induced inflammation: critical role of TNF receptor 1 signaling. J Immunol 1998;160(Suppl. 1):485–91.
[62] Constantin CE, Mair N, Sailer CA, Andratsch M, Xu ZZ, Blumer MJ, et al. Endogenous tumor necrosis factor α (TNFα) requires TNF receptor type 2 to generate heat hyperalgesia in a mouse cancer model. J Neurosci 2008;28(Suppl. 19):5072–81.
[63] Wajant H. The role of TNF in cancer. Death Rec Cognate Ligands Cancer 2009;49:1–15.
[64] Watkins LR, Goehler LE, Relton J, Brewer MT, Maier SF. Mechanisms of tumor necrosis factor-α (TNF-α) hyperalgesia. Brain Res 1995;692(Suppl. 1–2):244–50.
[65] Yang P, Allen MS, Aubry MC, Wampfler JA, Marks RS, Edell ES, et al. Clinical features of 5,628 primary lung cancer patients: experience at Mayo Clinic from 1997 to 2003. Chest 2005;128(Suppl. 1):452–62.
[66] Svobodník A, Yang P, Novotny PJ, Bass E, Garces YI, Jett JR, et al. Quality of life in 650 lung cancer survivors 6 months to 4 years after diagnosis. Mayo Clinic Proc 2004;79(Suppl. 8):1024–30.
[67] Ware JE, Kosinski M. SF-36 physical & mental health summary scales: a manual for users of version 1. Quality Metric Inc.; 2001.
[68] Colgrove LAA, Kim Y, Thompson N. The effect of spirituality and gender on the quality of life of spousal caregivers of cancer survivors. Ann Behav Med 2007;33(Suppl. 1):90–8.
[69] Land SR, Wickerham DL, Costantino JP, Ritter MW, Vogel VG, Lee M, et al. Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 2006;295(Suppl. 23):E1–10.
[70] Mosconi P, Cifani S, Crispino S, Fossati R, Apolone G. The performance of SF-36 health survey in patients with laryngeal cancer. Head Neck 2000;22(Suppl. 2):175–82.
[71] Petersen LR, Clark MM, Novotny P, Kung S, Sloan JA, Patten CA, et al. Relationship of optimism–pessimism and health-related quality of life in breast cancer survivors. J Psychosoc Oncol 2008;26(4):15–32.
[72] Belsey DA, Kuh E, Welsch RE. Regression diagnostics: identifying influential data and sources of collinearity. New York: John Wiley & Sons; 1980.
[73] Sarna L, Evangelista L, Tashkin D, Padilla G, Holmes C, Brecht ML, et al. Impact of respiratory symptoms and pulmonary function on quality of life of long-term survivors of non-small cell lung cancer. Chest 2004 Feb;125(2):439–45.
[74] Fortner BV, Okon TA, Portenoy RK. A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. J Pain 2002;3(Suppl. 1):38–44.
[75] Hwang SS, Chang VT, Kasimis B. Dynamic cancer pain management outcomes: the relationship between pain severity, pain relief, functional interference, satisfaction and global quality of life over time. J Pain Symptom Manage 2002;23(Suppl. 3):190–200.
[76] Anie KA, Steptoe A, Bevan DH. Sickle cell disease: pain, coping and quality of life in a study of adults in the UK. Br J Health Psychol 2002;7(Suppl. 3):331–44.
[77] Prucha E. Health reference series: cancer sourcebook. 3rd ed. Detroit (MI): Omnigraphics; 2000. p. 151–61.
[78] Wong WS, Fielding R. Quality of life and pain in Chinese lung cancer patients: is optimism a moderator or mediator? Qual Life Res 2007;16(Suppl. 1):53–63.