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Quality of Life: Socio-Demographic and Genetic Determinants as well as Links with Cancer Outcomes

Jeanne Pierzynski

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Quality of Life: Socio-Demographic and Genetic Determinants as well as Links with Cancer Outcomes

by

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Quality of Life: Its Socio-Demographic and Genetic Determinants and Associations with Cancer Outcomes

A

DISSERTATION

Presented to the Faculty of

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MD Anderson Cancer Center UTHealth

Graduate School of Biomedical Sciences

in Partial Fulfillment

of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

by

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Houston, Texas

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Dedication

To my parents (Joy and Gary Pierzynski) and brother (Garrison Pierzynski), for the unconditional love and support.

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Quality of Life: Its Socio-Demographic and Genetic Determinants and Associations with Cancer Outcomes

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Quality of life (QOL) is an independent prognostic factor for cancer. Lung cancer is the leading cause of cancer death. Breast cancer is the most diagnosed. Bladder cancer is the most expensive cancer to treat because of its high recurrence rate. We set to perform comprehensive analyses of predictors of QOL in these cancer sites with the future goal of improving QOL and outcomes.

In 6,456 newly diagnosed lung cancer patients, we investigated the relationship between baseline patient characteristics and QOL to identify determinants of QOL. A QOL questionnaire (SF-12v1) measured patients' physical component summary (PCS) and mental component summary (MCS). Factors that were associated with mean PCS and MCS included smoking status (PCS $P_{\text{trend}} < 0.001$; MCS $P_{\text{trend}} < 0.001$) and education (PCS $P_{\text{trend}} < 0.001$; MCS $P_{\text{trend}} < 0.001$). Genetic factors were also analyzed (in the p38 MAPK pathway). The homozygous rare genotype of *MEF2B*: rs2040562 showed an increased risk of poor MCS (OR: 3.06, 95% CI: 1.05-8.92, $P = 0.041$).

Next, in 10,681 newly diagnosed breast cancer patients, we found that physical QOL was associated with higher risks of recurrence and death. We identified determinants of QOL such as marital status and tumor size. We found that Hispanics and Blacks reported lower PCS and the determinants of poor QOL were disproportionally more common in minorities.

Finally, we investigated the associations between genetic variants in the dopaminergic pathway and clinical outcomes in bladder cancer patients. This pathway is closely related to depression (a QOL domain) and depressive symptoms at diagnosis are associated with bladder cancer mortality. Using a two-stage design (discovery and independent validation), we

identified several single nucleotide polymorphisms (SNPs) that was associated with recurrence or progression in non-muscle invasive bladder cancer overall or stratified by treatment.

In conclusion, we found important determinants of QOL in breast and lung cancer patients and racial disparities in breast cancer patients' QOL. This may contribute to racial disparities in breast cancer outcomes. Genetic variations in QOL-related pathways may modulate bladder cancer outcomes. These results provide a framework for identifying cancer patients at high risk for poor QOL and poor clinical outcomes.

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Chapter 1. Introduction

1.1. Overall Cancer Incidence and Mortality

1.1.1. Cancer Incidence

The overall cancer incidence in the U.S. is decreasing(1). When examined by sex, it is decreasing in men and remaining stable in women(1). It is estimated that men's cancer incidence has decreased approximately 2% per year based on the last decade of data(1). One reason for the decrease in cancer in men is thought to be due to decreases in PSA testing for men based on the U.S. Preventive Services Task Force recommendation because of the issue of over diagnosis and overtreatment of prostate cancer(2). Other potential reasons for the decrease in incidence in men are the decreases in diagnoses of lung and colorectal cancer(1). Women's cancer incidence trends for lung and colorectal are also decreasing, but the rates for breast, uterine, melanoma, and thyroid are increasing or staying stable(1). The reducing incidence of colorectal cancer in both men and women is largely due to an increase in colonoscopies and the removal of precancerous adenomatous polyps(1, 3).

1.1.2. Cancer Mortality

The overall mortality of cancer is also decreasing in U.S. This is seen across men and women, and a greater decrease is seen among the age group of 50-64 year olds(1, 4). Cancer mortality has decreased over the past two decades. This is due to the decrease in smoking rates and advances in cancer detection(1).

1.2 Lung Cancer

1.2.1. Lung Cancer Incidence and Risk Factors

It is estimated that approximately 243,170 men and women will be diagnosed with respiratory system cancer in the United States, with 222,500 of those being lung cancer in 2017(1). Slightly more men (116,990) than women (105,510) are estimated to develop lung cancer(1). It is the second most common cancer diagnosed in men and women(1). Lung cancer incidence is declining in men and women, but has declined approximately twice as quickly in men compared to women(1). This is mostly due to differences in smoking rates between men and women. Specifically, women began smoking later than men and at later ages and were slower to quit compared to men(5, 6).

The predominant risk factor for lung cancer is smoking and second hand smoke exposure(7). Men have higher incidences of lung cancer compared to women, and that is due to differences in tobacco usage(1, 8). Approximately 10-15% of lung cancer cases are in never smokers(9), which means there are other non-tobacco related risk factors. One such factor is radon exposure. Radon exposure is of concern to the general public due to indoor exposure and the potency of radon even when exposed to even small amounts(8). Certain occupational exposures also are risk factors for lung cancer. Asbestos exposure is a significant risk factor for lung cancer, as well as other occupational exposures such as arsenic and potentially silica(8, 10, 11). In addition, outdoor air pollution has been linked to increased lung cancer risk(8). This association is thought to be stronger in non-smokers(12, 13). Finally, there may be an association between diet and lung cancer risk. A recent study found that a diet with a high glycemic load or glycemic index (foods that cause a spike in blood sugar) was associated with an increased risk of lung cancer in non-Hispanic Whites. This association was seen stronger in non-smokers and patients with squamous cell carcinoma(14).

1.2.2 Lung Cancer Histology and Treatment

Lung cancers are typically classified in two categories: Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for 85% of all lung cancer diagnoses. Histology of NSCLC includes adenocarcinoma, large cell carcinoma, squamous cell carcinoma, and bronchioalveolar carcinoma(15). Approximately 13% of lung cancer diagnosed are SCLC(16), which also has a very poor prognostic outlook(15). Other rare types of lung cancer include mesothelioma and carcinoid tumors.

Treatment options vary depending on the type of lung cancer. SCLC patients usually receive chemotherapy with some going on to receive radiation therapy(16). For patients with stage I or stage II NSCLC, approximately 69% of patients receive surgery(16), with 25% of those patients going on to receive chemotherapy and/or radiation(16). NSCLC patients diagnosed with stage III or stage IV disease receive chemotherapy with some going on to receive radiation as well(16). Depending on the genetic mutations present in NSCLC patient's tumor, targeted therapy is an option as well. Potential targeted therapies include anaplastic lymphoma kinase (ALK) inhibitors and epidermal growth factor receptor (EGFR) inhibitors(16). Recent immunotherapies have also been developed that can be beneficial for NSCLC patients(16).

1.2.3. Lung Cancer Prognostic Factors and Clinical Outcomes

Lung cancer is a very deadly disease. Lung cancer survival depends on the stage at diagnosis. Patients diagnosed with localized disease from 2003 to 2009 had a five-year survival rate of 54% and that dropped down to 26% for regional stage and a dismal 4% for metastatic disease(17). When examining NSCLC and SCLC, SCLC has a five-year survival rate of 7% and NSCLC's five-year survival rate is 21%(16).

Prognostic factors can be grouped into two groups: clinical and host factors. Also, prognostic factors differ for different types of lung cancer. Clinical prognostic factors for NSCLC include poorly differentiated or undifferentiated carcinoma (poor survival), tumor genetic

markers such as EGFR or HER2 mutations (mutations that can be targeted for therapy which leads to better survival), the presence of metastasis, and ≥ 4 metastatic sites involved(18-20). Host characteristic prognostic factors for NSCLC include never smoking, age, sex (female sex is predictive of better survival), and performance status (a better performance status is predictive of better survival)(18, 20-22). Further, GWAS studies have shown promising results with variants showing association with survival in never smokers with NSCLC(23, 24). Recent research has also examined health-related quality of life (QOL) as a predictor of NSCLC lung cancer survival with promising results. A better QOL at time of diagnosis or within 6 months of it has been associated as an independent prognostic factor in lung cancer survival(25, 26) and is considered an important part of a lung cancer patient's comprehensive treatment plan. When examining prognostic factors for SLCL, extent of disease, sex, and performance status are independent factors for survival of SCLC(27, 28). Research has focused some on genetic predictors of survival, but the majority of this work has focused on NSCLC. Recently, the germline variant rs942190 in *TDPI* was associated with poor survival in SCLC patients(29).

1.3 Breast Cancer

1.3.1. Breast Cancer Incidence and Risk Factors

Breast cancer is the number one cancer diagnosed in women and the number two cause of cancer-related death in women, with approximately 252,710 women being diagnosed and 40,610 dying from the disease in the U.S. in 2017(1). The majority of breast cancers are diagnosed in women over the age of 59 (81%) and 89% of breast cancer deaths occur in this age range(30). Incidence rates increased in the 1980's and 1990's due to the increase in use of mammography screening and it is believed that those rates were inflated. A decrease in incidence was seen in the early 2000's due to a decrease in hormone therapy taken by menopausal women(30-33). The median age of diagnosis in women is 62 years of age and the median age of breast cancer death is 68 years of age(30). When examining racial disparities in breast cancer, Black women are diagnosed at a median age of 59, while white women are

diagnosed at an older median age of 63(30). The median age of breast cancer death in Black women is much lower than that in white women (62 years vs. 70 years). Black women show a lower incidence rate of breast cancer, but a higher mortality rate compared to non-Hispanic White women(30).

There is a significant amount of research that has examined risk factors for breast cancer. A seminal study from the Women's Health initiative found that estrogen use paired with progesterone as hormone therapy in menopausal women was a major risk factor for breast cancer(31). Reproductive factors associated with an increased risk of breast cancer include early age of menarche, late age of menopause, and nulliparity or later age at first pregnancy(34). Risk of breast cancer also increases as a women ages and it is estimated that a women's risk doubles every ten years until menopause(34). Mutations in genes *BRCA1* and *BRCA2* play a major role in many breast cancer cases in families with significant history of breast cancer(34). Finally, body mass index (BMI) (specifically obese and overweight women) is associated with an overall increased risk of breast cancer and this is consistently seen in postmenopausal women. Conflicting results have been shown in premenopausal women. Most studies have shown an inverse relationship between obesity and breast cancer risk in premenopausal women(35-37), but one study showed obesity as a risk factor in this same group(38). The inverse relationship in premenopausal women between BMI and breast cancer risk was only observed in Caucasian and Black women, but not Asian women, in whom there was a positive association between obesity and breast cancer risk(39).

1.3.2. Breast Cancer Molecular Subtype and Treatment

It is widely known that breast cancer is a very heterogeneous disease. Breast cancer is typically divided into two major molecular subtype groups: basal-like tumors and luminal A, luminal B, and HER2 enriched tumors(40). Basal-like tumors grow from basal/myoepithelial compartments and luminal A, luminal B, and HER2 enriched tumors grow from luminal cellular compartments(40). To further differentiate breast tumors, luminal A and luminal B tumors are

either estrogen receptor positive (ER-positive) and/or progesterone receptor positive (PR-positive). Further, luminal B tumors can also be HER2 positive(40). Basal-like tumors include triple-negative tumors which lack receptors for estrogen, progesterone, and HER2(40). Racial disparities also exist in terms of molecular subtype: premenopausal African Americans are more likely to be diagnosed with basal-like tumors (such as triple-negative, which have worse outcomes) and less likely to be diagnosed with luminal A tumors (which have a more favorable outcome)(41).

Women with local or regional breast cancer typically receive surgery (either breast conserving surgery or a mastectomy) followed by radiation therapy(16). Patients who are more likely to receive a mastectomy are those who have more advanced/aggressive tumors, are younger than the age of 40, or because radiation post-surgery is not recommended due to a previous condition(16, 42, 43). The majority of women with Stage III breast cancer will undergo a mastectomy instead of breast conserving surgery. Women diagnosed with Stage IV breast cancer receive chemotherapy and/or radiation(16). If a women has a hormone receptor positive tumor, most (79%) will receive hormone therapy(16).

1.3.3. Breast Cancer Prognostic Factors and Clinical Outcomes

Much of the research on predictors of breast cancer recurrence focus on molecular aspects of breast cancer. For example, women with triple-negative breast cancer have a higher risk of relapse and death within five years of diagnosis(44) and luminal A tumors tend to have better outcomes and lower rates of local or regional recurrence(45). In women with stage I or II breast cancer, vascular invasion from the tumor is associated with increased risk of local recurrence(46). Women with Stage I or II invasive breast cancer have a higher risk of recurrence if positive margins were found during surgery to remove the tumor(47). And high-grade tumors also are associated with a higher risk of recurrence following breast conserving surgery(48). When examining patient characteristics, age is a strong predictor of recurrence(49). One study found that women diagnosed with early stage breast cancer at

younger than the age of 35 showed a higher risk of recurrence(50). Racial disparities exist as well with recurrence of breast cancer. African American women are at a higher risk of recurrence compared to white women(51, 52).

There has been substantial research done on predictors of survival in breast cancer patients. Two of the most significant prognostic factors are tumor size and lymph node status(53). Other major prognostic factors include estrogen receptor/progesterone receptor status, with the presence of the receptors correlating with better survival(54, 55). Some research suggests that the effect of hormone receptor on survival is not long term and this may be due to the positive receptor status causing breast tumors to grow slower(56). Another major prognostic factor is the overexpression of HER2/neu in breast tumors. Overexpression of HER2/neu is associated with a more aggressive breast tumor, higher rates of recurrence, and higher rates of death in patients with positive lymph node tumors(57). Finally, recently published studies also include prognostic models for potential predictors of recurrence and survival of breast cancer(58).

Recurrence rates differ based on type of breast cancer and treatment. For example, women with breast cancer who received breast-conserving therapy only had a 10-year risk of locoregional or distant recurrence rate of 35%, and with receiving radiation therapy that risk decreased to 19.3%(59). When examining specific subtypes of breast cancer, triple-negative breast cancer has a significant increased risk of recurrence within the first five-years(44). Breast cancer survival rates have been improving. From 1989 to 2014, the death rate decreased by 38% for breast cancer(1). Women diagnosed with localized disease have a five-year survival rate of 99%(1). When the disease is diagnosed regionally, that percentage drops to 85%(1). And women diagnosed with distant disease have a five-year survival rate of 26%(1). When examining racial disparities in breast cancer survival, Asian/Pacific Island (PI) women have the highest five-year breast cancer survival (overall and for each stage at diagnosis). And Black women have the lowest five-year breast cancer survival. When looking at mortality trends

by race, from 2003-2012 breast cancer mortality rates declined by 1.8% in whites, 1.5% in Hispanics, and 1.0% in Asian/PI (60).

1.4. Bladder Cancer

1.4.1. Bladder Cancer Incidence and Risk Factors

Bladder cancer is a cancer that affects men more than women and incidence and death rates are approximately four-fold higher in men(1). This makes it the estimated fourth most diagnosed cancer and the eighth cause of cancer related death in men in the U.S. in 2017. Approximately 60,490 men will be diagnosed and 12,240 men will die from the disease(1). Bladder cancer incidence rates have been consistent over time.

The most significant environmental and modifiable risk factor for bladder cancer is smoking(61-63). Another established environmental risk factor for bladder cancer is occupational exposures to aromatic amines(64). A family history of bladder cancer is also a risk factor(65), and family members with a first-degree relative diagnosed have a two-fold increased risk of developing the cancer(66). Genetic variations in candidate genes have been recognized as risk factors as well. For example, *NAT2* slow acetylator genotype has been found to increase the risk of bladder cancer by 40%(67, 68). Also, it is well recognized that the *GSTM1*-null phenotype is associated with an increased risk of bladder cancer(67, 69). Single nucleotide polymorphisms (SNPs) in several genes have also been associated with susceptibility to bladder cancer. For example, rs2294008 in *PSCA* located on 8q24.3 was discovered via a genome-wide association study (GWAS) and was associated with a 1.15-fold increased risk of bladder cancer (OR=1.15, 95% CI: 1.10-1.20, P=2.14x10⁻¹⁰)(70). Other variants associated with bladder cancer susceptibility include *MYC*: rs9642880, *TP63*: rs710521, *FGFR3*: rs798766, *CLPTM1L*: rs401681, *TERT*: rs2736098, rs1014971, *CCNE1*: rs8102137, and *UGT1A*: rs11892031(67).

1.4.2. Bladder Cancer Histology and Treatment

The majority of bladder cancers diagnosed in Western nations are urothelial carcinomas (transitional cell carcinoma)(67). Bladder cancer can be broadly categorized as non-muscle invasive bladder cancer (NMIBC) or muscle invasive bladder cancer (MIBC). NMIBC is bladder cancer that has not invaded the muscle layer of the bladder and MIBC has invaded the muscle layer of the bladder(71).

Standard treatment for patients diagnosed with NMIBC is transurethral resection (TUR). Typically TUR is followed with intravesical chemotherapy such as Bacillus Calmette-Guerin (BCG)(72, 73) with the goal of preventing or delaying recurrence or progression of disease. Patients diagnosed with MIBC typically have a cystectomy and then receive chemotherapy and/or radiation(74).

1.4.3. Bladder Cancer Prognostic Factors and Clinical Outcomes

NMIBC and MIBC have common and distinct prognostic factors. For NMIBC, factors that are considered predictors of recurrence and/or progression are tumor size, number of tumors, prior recurrence rate, T category, grade, presence of carcinoma in situ(75). For patients with MIBC, prognostic factors include small tumor size, papillary histology, absence of hydronephrosis, a complete response to induction chemotherapy, and a complete TUR that is visible(76).

Patients with NMIBC face a high risk of recurrence, as 50-80% of patients experience a recurrence(77). Of those patients, approximately 14% go on to progress to MIBC after receiving TUR(77) and overall 20-30% of NMIBC progress to a higher grade or stage(71). This indicates that the majority of patients diagnosed with MIBC are diagnosed without a prior history of superficial disease(78). When analyzing survival statistics in bladder cancer patients, survival statistics are divided by NMIBC and MIBC. NMIBC patients fare well in terms of survival. Patients who are diagnosed with NMIBC low-grade disease Ta do not have a 15-year cancer-specific mortality(79, 80). Patients diagnosed with high-grade Ta tumors have a 15-year disease specific survival of 74%(79, 80). Patients diagnosed with T1 tumors have a 15-

year disease specific survival of 61%(79, 80). When examining MIBC survival statistics, the outlook is not as favorable. Patients with MIBC have a 50% five-year survival rate after cystectomy(81). If a patient has a T3 (has invaded into the fatty layer outside of the bladder) or T4 (spread locally beyond the bladder) tumor, the five-year survival decreases to between 25-35%(81).

1.5 Quality of Life

1.5.1. Quality of Life Overview

QOL has become increasingly important for cancer patients and their treatment. It is a comprehensive concept that spans many domains of a patient's well-being. QOL is subjective and includes cognitive, psychosocial, emotional, spiritual, social, and physical domains domains(82). When patients are faced with a diagnosis of cancer, psychosocial stress is a major product of the diagnosis and it is expected that changes in QOL will occur, but a new cancer diagnosis does not account for all the inter-individual variation in QOL that is seen in newly diagnosed cancer patients(82, 83). QOL is important to understand because it can lead to meaningful clinical changes in cancer patients(84).

1.5.2. QOL Measures

Quality of life is measured by a validated questionnaire. There are many measures for quantifying QOL, including questionnaires that measure general QOL in many populations(85) or are disease specific (such as cancer)(86). Research has supported that there is no difference in responsiveness or accuracy of capturing QOL changes between using general questionnaires or disease specific(87). One questionnaire that is used for many different populations is the Short-Form 12 version 1 (SF-12v1). The SF-12v1 is a 12 question measure that was derived from the SF-36 questionnaire(88). It encompasses four domains of QOL (physical, social, functional, and emotional) and eight subscales (physical functioning, general health, bodily pain, role physical, vitality, social functioning, role emotional, and mental health)(89). When scored, the questionnaire is normalized to a mean of 50, which is based on the US general population. A higher score indicates a better QOL.

1.5.3. Determinants of QOL

Patient determinants (host and clinical) can impact a patient's QOL(83, 90, 91). Few studies have examined QOL in a group comprised of many cancer sites. For example, a study comprised of 351 patients (with approximately 9% of patients currently undergoing chemotherapy or radiation) with breast, gynecologic, urologic, and gastrointestinal cancers examined determinants of QOL(83). This study discovered that when examining physical QOL domains, patients who were men, did not have recurrent cancer, and were not in active treatment reported better physical QOL(83). When examining mental QOL, patients who had good social support, a higher education level, were older, married, and did not have advanced disease reported better mental QOL(83).

Many studies have examined specific cancer sites. For example, patients who continue to smoke cigarettes after being diagnosed with advanced lung cancer report worse QOL compared to patients who quit smoking cigarettes after diagnosis(92). Another study from Mayo Clinic examined marital status and QOL in lung cancer patients. While marital status at diagnosis was not associated with QOL overall, there were interesting associations when examining specific domains of QOL(90). Specifically, patients that were widowed and married at diagnosis scored better on social support and spirituality than single and divorced patients(90). Another study examining QOL in 101 newly diagnosed lung cancer patients (within three months of their diagnosis) found that self-efficacy was a strong predictor of QOL(93). Many of the studies published on QOL in lung cancer patients are plagued by small sample sizes and lack of detailed demographic data. To our knowledge, there currently lacks an in-depth comprehensive analysis of determinants of QOL in newly diagnosed lung cancer patients.

There are many studies that examined predictors of QOL in breast cancer patients, though many examined QOL issues in long-term breast cancer survivors. A prospective study using the survivors of breast, colorectal, and endometrial cancer in the Iowa Women's Health Study established that persistent smokers were more likely to report poor physical functioning(94). A

study examined how QOL changes throughout treatment and found that women who were less than 60 years of age or had a psychiatric morbidity were more likely to report poor QOL at diagnosis before treatment(95). Another study also found that younger age (<50) was associated with poor QOL(96). Racial disparity in breast cancer patients is an important issue and this issue expands into QOL. For example, African American breast cancer survivors are more likely to report poor physical function compared to Caucasian patients in unadjusted models(97). This is thought to be attenuated by factors such as BMI(97). In a comprehensive study that examined QOL differences among races, lower acculturated Latinas had lower functional well-being and emotional well-being (domains of QOL) compared to Whites. And African Americans reported better emotional well-being compared to Whites(96). While research supports racial disparities in QOL in breast cancer patients, more research is needed to understand predictors of this disparity.

Recent research has suggested that depression (a domain of QOL) is an important component of survival in cancer patients(98). It is estimated that the prevalence of depression in cancer patients ranges from 13% to 40% and that a significant number of patients have depressive symptoms without meeting the threshold criteria for depression(98, 99). Depression and anxiety can lead to poor outcomes after surgery and hinder post-surgery healing(100). When looking at cancer specific studies, current depressive symptoms at time of bladder cancer diagnosis was associated with poor overall survival(101). And studies suggest that up to 42% of bladder cancer patients report depression(102, 103). The mechanism behind this finding is not clearly understood but is hypothesized that increased mortality could be related to neuroendocrine and immunological mechanisms(101, 104, 105).

1.5.4. Genetic Predictors of QOL

Research supports a genetic component to QOL in cancer patients. A majority of the work has been done in lung cancer populations. A study from Mayo clinic analyzed 470 SNPs in 56 genes(106). A total of six SNPs on four genes were validated and associated with QOL and QOL domains in lung cancer patients in adjusted and unadjusted models (*MGMT*: rs38538300,

MGMT: 10741191, *MGMT*: rs3852507, *GSTZ1*: rs2287396, *ABCC4*: rs9524885)(106). Another study examined genetic variants and the association with pain severity in lung cancer patients(107). This study found that a variant in *IL-8* was associated with significant pain in white lung cancer patients(107). Finally, another study examined QOL and pro- and anti-inflammatory cytokine genetic variants in a mixed cancer population (breast, lung, and brain)(108). The results suggested that SNPs in interleukin 1 receptor 2 (*IL1R2*) were associated with lower QOL (when QOL was dichotomized as high and low) and SNPs in nuclear factor kappa beta 2 (*NFKB2*) were also associated with lower QOL(108). Inflammatory related pathways are an important area to examine when examining genetics and QOL in cancer patients because the biologic mechanism of inflammation is an important part of QOL as well as cancer clinical outcomes(109-111). For example, increased circulating levels of pro-inflammatory cytokines have been found in newly diagnosed cancer patients. These increased levels of cytokines can pass into the central nervous system (CNS) and cause increased psychobehavioural symptoms such as fatigue and depression which can negatively impact QOL(111). Further, activation of inflammatory pathways, such as the p38 MAPK pathway, can alter neurotransmitter function in the CNS which can have negative impacts of domains of QOL such as depression(112).

Another area of research focus is in genetics and domains of QOL, like depression. Depression is an important component of QOL in cancer patients. As discussed above, the study regarding depressive symptoms in newly diagnosed bladder cancer patients and overall survival lead to the question “Could there be a genetic component to these findings?”(101). A pathway of interest to examine genetic predictors of depression and poor clinical outcomes in bladder cancer patients is the dopamine pathway. There are four main dopamine pathway in the brain: Nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular(113). Dopamine is synthesized from tyrosine in the cytoplasm of presynaptic neurons and when released dopamine interacts with one of five dopamine receptors in the postsynaptic neuron(114). The dopamine receptors are divided into two groups: the dopamine 1 (D1) family which is made up

of D1 and D5 subtypes and the D2 family (made up of D2, D3 and D4 subtypes). The D1 receptors increase intracellular cyclic adenosine monophosphate (cAMP) concentrations and also activate secondary messenger pathways(114). The D2 family reduces adenylate cyclase activity and can assist in controlling release of dopamine(114). The dopamine system plays many roles that are vital to human function such as voluntary movement, feeding, affect, sleep, reward, and working memory(113). Dopamine also functions in the periphery and regulates renal function and cardiovascular functions among other systems(115). Mental health disorders such as depression, schizophrenia, attention deficit hyperactivity disorder (ADHD), and bi-polar depression are associated with the dopamine system(113, 114). The association with depression is what makes this pathway of interest for this current study as well as the evidence of dopamine receptor expression in the bladder wall (*DRD1* and *DRD2*)(116).

1.5.5. QOL and Survival in Cancer Patients

One reason that QOL is so important in cancer patients is because of the association between QOL and survival. Specifically, QOL is considered a prognostic indicator in cancer patients, with a better QOL associated with better survival(117). This has been seen in populations of mixed cancer types(117) as well as cancer site specific studies(118-121). The importance of QOL as a prognostic factor for survival in cancer patients is that interventions can be targeted to improve QOL with the hopes of improving survival and improving the patient's cancer experience. An example of one such intervention was done in patients with advanced cancer receiving radiotherapy(82). The QOL intervention arm of this trial saw significant improvements in QOL scores compared to the group that did not receive the intervention(82). This highlights the importance of understanding the complicated subject of QOL in cancer patients.

1.6 Hypotheses

The work was conducted with the following hypotheses in mind:

Hypothesis I: QOL varies by demographic and clinical characteristics in newly diagnosed lung cancer patients.

Hypothesis II: To determine the association between QOL and survival in breast cancer patients as well as characterize determinants of QOL among racial groups in breast cancer patients.

Hypothesis III: To determine the association between genetic variants in a pathway involved in inflammation and depression and QOL in a subset of newly diagnosed cancer patients.

Chapter 2. Socio-demographic, Clinical, and Genetic Determinants of Quality of Life in Lung Cancer Patients

2.1. Introduction

Newly diagnosed lung cancer patients experience one of the worst symptom burdens(122). Symptom burden and poor prognosis underscore the need to better understand the mediating factors that impact both and the potential relationship among the two adverse outcomes. In recent years, health-related quality of life (QOL) has become an important aspect of cancer treatment and research has linked improved patient-reported QOL to improved lung cancer survival(121, 123).

To date, several studies have investigated the role of demographic factors on QOL in cancer patients. For example, African American men recently diagnosed with prostate cancer and African American women breast cancer survivors reported better emotional well-being compared to Caucasians(96, 124). Older age has been shown to be a strong predictor of emotional and physical well-being for a variety of cancer sites, including late-stage gastrointestinal, genitourinary, breast or gynecological cancer, lung, pancreatic, or esophageal cancer (125).

Previous studies suggested that women with lung cancer report higher rates of depression prior to treatment (49%) than men (29%), and that depression is a strong indicator of QOL(126, 127). In small cell lung cancer (SCLC) patients, one study showed that late quitters (those smoking one year post diagnosis) exhibited the worst QOL compared to all other smoking categories(128), while another study reported inconsistent findings with persistent smokers (those who continue to smoke following diagnosis) reporting worse QOL(129). While evidence suggests that demographic characteristics are predictors of cancer patient QOL, inter-individual variability still remains, which may be explained by clinical factors. For example, SCLC patients reported worse depression and anxiety than non-small cell lung cancer (NSCLC) patients(126).

Genetic components may also affect QOL and therefore impact survival in lung cancer patients. However, there are a limited number of studies that have explored this hypothesis in lung cancer. For example, one study reported an association between three single nucleotide polymorphisms (SNPs) in two genes related to inflammation (*LTA* and *PTGS2*) and pain

severity, social functioning, and mental health in 3-5 year lung cancer survivors(130). The p38 MAPK pathway is activated through extracellular stimuli such as pro-inflammatory cytokines including interleukin (IL)-1 and tumor necrosis factor (TNF) alpha(131). Once the p38 MAPK pathway is activated, the downstream effects ultimately result in changes in cell survival through programmed cell death(132) and pathway activation can lead to the increased production of more pro-inflammatory cytokines(133). This pathway is of interest in regards to QOL because it is a key mediator of response to cellular and environmental stress. Examples of stress that activate this pathway are pro-inflammatory cytokines (as stated above, such as IL-1 and TNF-alpha (which can then produce more pro-inflammatory cytokines)), which have been associated with negative symptoms in cancer patients (such as fatigue and depression) of which can negatively impact QOL(111). To date, no study has examined genetic variation in this pathway in relation to QOL in lung cancer patients.

Since 1999, lung cancer patients at MD Anderson Cancer Center have completed the SF-12 general health-related QOL questionnaire at their first clinic visit, providing an opportunity to systematically investigate the factors that contribute to variation in QOL at diagnosis in a large group of lung cancer patients. The availability of DNA for genetic analyses and extensive clinical and follow-up information also allowed for assessment of the role of genetic variation on QOL and relationship with survival. The findings provide a better understanding of baseline QOL factors affecting lung cancer patients and potentially set the stage for behavioral interventions to improve both QOL and survival.

2.2. Methods

2.2.1. Study Population

The population for the current analysis included 6,420 newly diagnosed lung cancer patients with a diagnosis of a tumor of the lung according the World Health Organization (WHO) classification (this includes SCLC and NSCLC) from The University of Texas MD Anderson Cancer Center. Study participants included those that completed an institutional patient health intake questionnaire at their initial visit to MD Anderson within one year of diagnosis.

For exclusion criteria, individuals with multiple primary tumors were excluded, except for multiple lung tumors. The participants provided written informed consent and the study was approved by the Institutional Review Board.

2.2.2. Data Collection

The SF-12v1 is part of MD Anderson's institutional patient intake questionnaire completed by all new patients at MD Anderson Cancer Center, which also includes demographic and epidemiological data. The SF-12v1 had 8 subscales that are measured (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health), and these subscales were used to calculate the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores(89). Both the MSC and PCS were normalized to a mean of 50 (SD=10) based on responses to the SF-12v1 among the US general population. A higher score (greater than 50) indicated a QOL that is better than the general population. The question in the SF-12v1 that asks "During the past 4 weeks, how much did pain interfere with your normal work" was modified in our patient intake questionnaire as "During the past week, has pain interfered with your general activities" and the scoring was adjusted to match the SF-12v1 scoring.

Race was self-reported by the study participants. Race was classified as "White, Anglo", "Hispanic Origin" "Black" "Asian/Pacific Islander" and "Other". Smokers were classified into three groups: "never", "yes, but quit", and "yes, currently" and was self-reported. Never

smokers were defined as individuals who had smoked less than 100 cigarettes in their lifetime. Alcohol usage was divided into three groups: never, former and current drinkers (having one or more drink per week). Participants had a positive past medical history if they self-reported a previous diagnosis of heart or lung problems, diabetes, high blood pressure, liver problems, thyroid problems, kidney problems, frequent infections, stroke, bleeding problems, HIV/AIDS, seizures, circulation problems, and any psychological or psychiatric problems.

Pathological features, treatment, and survival data were obtained from MD Anderson's Tumor Registry for all study participants.

2.2.3. DNA Isolation and Genotyping

A subset of patients (N=641) were previously enrolled in an ongoing lung cancer epidemiology study which allowed us to analyze 218 SNPS in 20 genes from the p38 MAPK pathway. DNA isolation and genotyping methods have been previously described(134, 135). In short, inflammation pathway-related genes were identified through the Gene Oncology Database(136, 137) and the National Center for Biotechnology Information (NCBI) Pubmed(138). Haplotype tagging SNPs were selected for each gene 10 kb upstream of the transcriptional start site or 10 kb downstream of the transcriptional stop site. SNPs in the coding (nonsynonymous SNPs and synonymous SNPs) and regulatory regions (splicing site, promoter, 5'UTR, and 3'UTR). In addition, SNPs previously reported to be associated with cancer and functional SNPs were included. Genotyping was completed using the Illumina Infinium iSelect HD Custom Genotyping BeadChip.

2.2.4. Statistical Analysis

To analyze the difference in mean PCS and MCS scores between categories of host characteristics, t-test or ANOVA with pairwise comparison testing was used (SIDAK test). PCS and MCS were dichotomized by 50 (previously established cut-off) to assess the association of demographic and clinical variables with QOL. Unconditional multivariate logistic regression was used to calculate odd ratios (ORs), 95% confidence intervals (CIs), and P values. Confounders were adjusted for in the PCS and MCS multivariable models and included age, sex, education

level, race, marital status, alcohol use, smoking status, history of past medical event, histology, cancer stage, and prior treatment for current or previous cancer. A sensitivity analysis was completed and found no major differences between the full data (with missing stage categorized as unknown) and the reduced data (with missing stage removed) (data not shown). Therefore, the full dataset was used. For the effect of 218 SNPs in the p38 MAPK pathway on PCS and MCS risk, multivariate unconditional logistic regression was used to estimate ORs and 95% CIs. Dominant, recessive, and additive models of inheritance were assessed for each SNP. The study sample was divided into two groups by assigning alternating samples into the discovery set and the validation set, with the first group analyzed in a discovery phase and the significant variants from the discovery phase were checked for validation in the second group as validation phase (adjusting for the same factors as described above). Multivariate Cox regression was used to estimate hazard ratios (HR) and 95% CI for all survival analyses. The proportional hazards was examined by graphing $\log(-\log(\text{survival}))$ versus log of survival time. The effects of PCS and MCS scores on five-year lung cancer survival (calculated using the diagnosis date and last contact date) were estimated, adjusting for age, sex, race, smoking status, histology, cancer stage, prior cancer treatment, and treatment at MD Anderson. Kaplan-Meier survival curves and log-rank tests were calculated to analyze the difference in five-year survival times between PCS and MCS scores and stage. The association between genetic variants in the p38 MAPK pathway and five-year survival was calculated in the dominant, recessive, and additive models of inheritance, adjusting for age, sex, smoking status, histology, stage, surgery (yes/no), radiation (yes/no), chemoradiation (yes/no), and pre-treatment performance status. Additional factors were adjusted for in the genetic survival analysis because data was available for those covariates. Discovery and validation analyses were completed as described above. Statistics were completed using STATA 13 (Stata Corporation, College Station, TX) statistical software. A P value of less than 0.05 was considered statistically significant. VEGAS software was used to perform a gene-based interaction analysis(139). A P value of <0.05 was significant. In the VEGAS analysis, significant variants were carried forward

and the validation set was analyzed using the same model that was most significant in the discovery phase.

2.3. Results

2.3.1. Host Characteristics

The patient characteristics are shown in **Table 1**. The majority of the patients were 60 to 69 years of age, with a mean age of 60.9 years. Most patients were married (72.9%) and had completed at least a high school education (57.7%). White patients made up the largest racial group. Among the smoking status groups, 1,112 patients were never smokers, 4,083 patients were former smokers and 1,197 patients were current smokers. Also, most patients reported never consuming alcohol (41.2% of patients). In addition, 621 patients were diagnosed with stage I lung cancer, 228 were diagnosed with stage II, 979 were diagnosed with stage III, and 1,768 patients were diagnosed with stage IV lung cancer. The distribution of PCS and MCS scores in the study population is seen in **Figure 1**. The distribution of PCS and MCS scores in the study population show that neither the PCS nor MCS scores are normally distributed. The patient characteristics for the sub population that are part of the on-going lung cancer epidemiology study with genetic information is seen in **Table 2**.

Table 1. Host Characteristics and the Association of Demographic, Lifestyle, and Clinical Characteristics with PCS and MCS Score

Characteristic	N	%	PCS, Mean (SD)	P value	MCS, Mean (SD)	P value
Age						
<50	1,081	16.84	39.05 (11.60)		45.37 (10.89)	
50-59	1,672	26.04	39.12 (11.95)	1.000	44.57 (11.33)	0.351
60-69	2,149	33.47	38.50 (11.93)	0.759	46.23 (11.35)	0.221
70+	1,518	23.64	38.44 (11.59)	0.715	47.48 (11.45)	<0.001
P for trend				0.066		2.1x10 ⁻¹⁰
Sex						
Male	3,431	53.46	38.96 (11.90)		46.75 (11.33)	
Female	2,987	46.54	38.49 (11.69)	0.109	45.03 (11.29)	<0.001
Marital status						
Married	4,679	72.93	39.24 (11.75)		46.33 (11.19)	
Widowed	635	9.90	37.00 (11.73)	<0.001	45.83 (11.84)	0.972
Separated	34	0.53	36.06 (11.91)	0.710	42.19 (11.27)	0.290
Divorced	637	9.93	37.24 (11.64)	0.001	44.13 (11.66)	<0.001
Never Married	431	6.72	38.23 (12.30)	0.606	44.96 (11.37)	0.154
Education						
<High School	760	12.37	35.17 (11.22)		42.63 (11.81)	
High School/Vocational/AA	3,543	57.66	38.02 (11.60)	<0.001	45.85 (11.45)	<0.001
College Degree	1,842	29.98	41.77 (11.71)	<0.001	47.64 (10.59)	<0.001
P for trend				1.1x10 ⁻⁴⁶		7.1x10 ⁻²⁴
Race						
White	5,268	83.09	38.92 (11.75)		45.97 (11.34)	
Hispanic	280	4.42	39.05 (11.73)	1.000	44.56 (11.71)	0.355
Black	460	7.26	35.73 (11.97)	<0.001	45.21 (11.40)	0.849
Asian/Pacific Islander	217	3.42	40.62 (11.54)	0.316	48.26 (10.68)	0.034
Other	115	1.81	37.80 (12.21)	0.976	47.27 (10.90)	0.918
Alcohol						
Never	2,626	41.19	37.19 (11.50)		45.48 (11.58)	
Former	1,205	18.90	35.37 (11.21)	<0.001	44.48 (11.58)	0.033
Current	2,544	39.91	41.93 (11.64)	<0.001	47.14 (10.86)	<0.001
P for trend				2.3x10 ⁻⁴⁷		1.6x10 ⁻⁷
Smoking						
Never	1,112	17.40	40.78 (11.86)		48.02 (10.51)	
Former	4,083	63.88	38.85 (11.73)	<0.001	46.06 (11.29)	<0.001
Current	1,197	18.73	36.47 (11.65)	<0.001	43.61 (11.88)	<0.001
P for trend				1.2x10 ⁻¹⁸		5.4x10 ⁻²¹
Past Medical History						
Yes	5,394	84.43	38.37 (11.78)		45.81 (11.45)	
No	995	15.57	40.61 (11.80)	<0.001	46.73 (10.66)	0.018
Past Cancer Treatment						
Yes	1,845	28.74	35.86 (10.62)		45.39 (11.15)	
No	4,575	71.26	39.90 (12.06)	<0.001	46.17 (11.41)	0.012
Histology						

Non-Small Cell Carcinoma							
Adenocarcinoma	2,996	49.32	39.66 (11.82)		46.63 (11.08)		
Squamous Cell	973	16.02	38.03 (11.46)	0.003	45.69 (11.73)	0.305	
Large Cell	208	3.42	37.36 (11.33)	0.091	45.00 (11.30)	0.500	
Non-small cell carcinoma, non-specified	972	16.00	37.40 (11.85)	<0.001	45.20 (11.38)	0.009	
Small Cell	667	10.98	36.84 (11.67)	<0.001	43.77 (11.62)	<0.001	
Other	258	4.25	41.51 (11.92)	0.200	47.65 (11.37)	0.930	
Stage							
I	621	9.67	43.90 (11.46)		49.28 (10.39)		
II	228	3.55	43.68 (11.74)	1.000	50.09 (10.37)	0.988	
III	979	15.25	41.16 (11.79)	<0.001	46.26 (11.21)	<0.001	
IV	1,768	27.54	37.74 (11.82)	<0.001	45.22 (11.52)	<0.001	
Unknown	2,824	43.99	37.00 (11.30)	<0.001	45.23 (11.34)	<0.001	
P for trend				9.2x10 ⁻⁴²		2.3x10 ⁻¹¹	

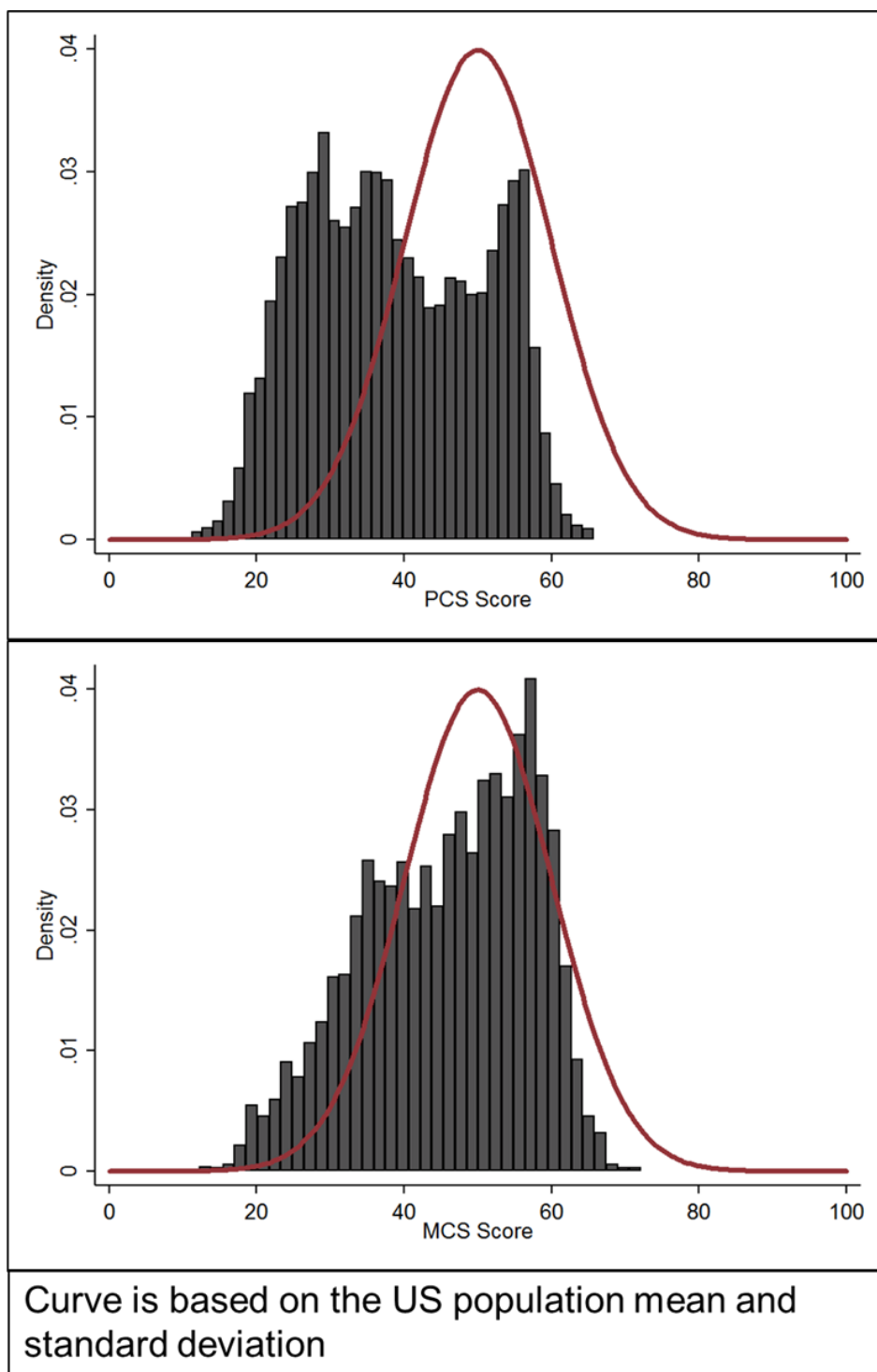


Figure 1. Distribution of PCS and MCS scores in the lung cancer study population

Table 2. Host Characteristics of Subset Population Analyzing the p38 MAPK Pathway

Characteristics	Discovery, N (%)	Validation, N (%)	P-Value
MST	22.3 Months	20.4 Months	
Age, Mean(SD)	61.6 (10.9)	61.8 (11.0)	0.82
Survival Time, Mean(SD)	28.3 (21.5)	27.7 (22.2)	0.71
Sex			
Male	154 (48.0)	166 (51.9)	
Female	167 (52.0)	154 (48.1)	0.32
Marital Status			
Married	239 (74.5)	243 (75.9)	
Widowed	36 (11.2)	32 (10.0)	
Separated	1 (0.3)	2 (0.6)	
Divorced	32 (10.0)	29 (9.1)	
Never Married	13 (4.1)	14 (4.4)	0.94
Education			
<High School	30 (9.6)	28 (9.0)	
High School, Voc, AA	203 (64.9)	199 (64.2)	
College Degree	80 (25.6)	83 (26.8)	0.93
Smoking Status			
Never	82 (25.6)	80 (25.1)	
Former	189 (59.1)	191 (59.9)	
Current	49 (15.3)	48 (15.1)	0.98
Alcohol Use			
Never	146 (45.5)	136 (42.8)	
Former	38 (11.8)	42 (13.2)	
Current	137 (42.7)	140 (44.0)	0.75
Previous Treatment			
Yes	28 (8.7)	23 (7.2)	
No	293 (91.3)	297 (92.8)	0.47
Past Medical History			
Yes	281 (87.5)	268 (84.5)	
No	40 (12.5)	49 (15.5)	0.27
Histology			
Adenocarcinoma	176 (57.3)	177 (57.5)	
Squamous Cell	52 (16.9)	51 (16.6)	
Other	79 (25.7)	80 (26.0)	0.99
Stage			
I	62 (21.2)	52 (18.3)	
II	21 (7.2)	21 (7.4)	
IIIA	50 (17.1)	40 (14.0)	
IIIB	31 (10.6)	29 (10.2)	
IV	129 (44.0)	143 (50.2)	0.62
Surgery			
No	218 (71.7)	220 (73.8)	
Yes	86 (28.3)	78 (26.2)	0.56
Radiation			
No	235 (77.3)	222 (74.5)	
Yes	69 (22.7)	76 (25.5)	0.42
Chemotherapy			
No	160 (52.6)	146 (49.0)	
Yes	144 (47.4)	152 (51.0)	0.37
Chemotherapy/Radiation			
No	241 (79.3)	260 (87.3)	
Yes	63 (20.7)	38 (12.8)	0.009
Performance Status			
0	75 (24.7)	84 (28.2)	
1	125 (41.1)	141 (47.3)	

	2-4	37 (12.2)	41 (13.8)	
	Unknown	67 (22.0)	32 (10.7)	0.003
PCS				
	≥50	99 (30.8)	101 (31.6)	
	<50	222 (69.2)	219 (68.4)	0.84
MCS				
	≥50	152 (47.4)	154 (48.1)	
	<50	169 (52.7)	166 (51.9)	0.84
Vital Status				
	Alive	85 (26.5)	96 (30.0)	
	Dead	236 (73.5)	224 (70.0)	0.32

2.3.2. Relationship between Demographic and Clinical Characteristics and PCS/MCS Scores

Comparison of Mean PCS Scores

Table 1 shows the mean PCS score results. Patients who had a college degree (41.8, $P<0.001$) reported a statistically significantly higher mean PCS score when compared to individuals with less than a high school education (35.2). Interestingly, current drinkers had a higher mean PCS (41.9, $P<0.001$) score compared to never drinkers (37.2). The opposite effect was seen for current smokers, who showed a lower mean PCS (36.5, $P<0.001$) score when compared to never smokers (40.8). When examining racial differences, Blacks were more likely to have a low mean PCS (35.7, $P<0.001$) score compared to whites (38.9). The mean PCS score for widowed patients (37.0, $P<0.001$) was significantly lower compared to those currently married (39.2). The PCS scores for patients with squamous cell (38.0, $P=0.003$) and small cell (36.8, $P<0.001$) lung cancer were lower than those with adenocarcinoma (39.7). When stratifying by smoking (never or ever), patients who have ever smoked diagnosed with small cell lung (36.8, $P<0.001$) cancer reported worse PCS scores compared to those diagnosed with adenocarcinoma (39.2) (data not shown). Never smokers diagnosed with small cell lung cancer did not report significantly worse PCS scores compared to patients diagnosed with adenocarcinoma. Finally, stage III (41.2, $P<0.001$) and stage IV (37.7, $P<0.001$) lung cancer patients reported worse PCS scores compared to those with stage I (43.9).

Poor PCS Risk

The results for the adjusted risk analysis are shown in **Figure 2** and **Appendix: Supplemental Table 1**. Education was significantly associated with risk of reporting a poor PCS. When compared to less than a high school education patients with a college degree had a lower risk of reporting a low PCS (OR=0.50, 95% CI: 0.39-0.64, $P=8.7\times10^{-8}$). Smoking status was also significantly associated with PCS. When compared to never smokers, former smokers had a higher risk of reporting a poor PCS (OR=1.34, 95% CI: 1.11-1.61, $P=0.002$). Current smokers (compared to never smokers) had an even larger increased risk of reporting a poor

PCS (OR=1.81, 95% CI: 1.43-2.31, $P=1.3 \times 10^{-6}$). When examining clinical characteristics, squamous cell lung cancer patients were at a 41% increased risk of a poor PCS (OR =1.41, 95% CI: 1.16-1.72, $P=0.001$). Individuals diagnosed with stage III (OR=1.45, 95% CI: 1.15-1.84, $P=0.002$) and IV (OR=2.79, 95% CI: 2.23-3.50, $P<1.0 \times 10^{-63}$) lung cancer are at an increased risk of an unfavorable PCS score. Stage IV lung cancer patients showed the largest risk of a poor PCS of all determinants in the model.

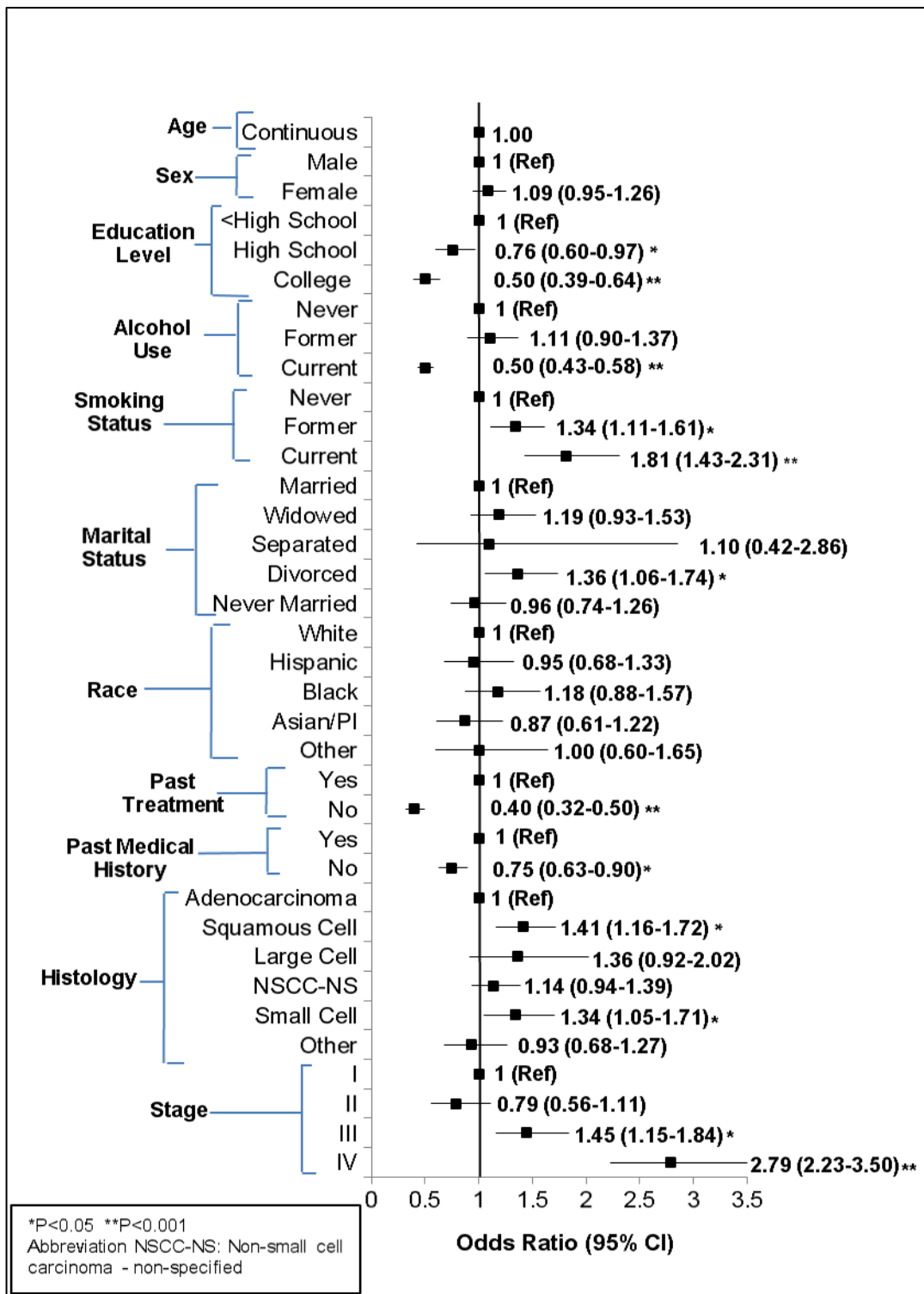


Figure 2. Association between demographic/clinical Factors and PCS in lung cancer patients.

Odds ratios adjusted by age, sex, race, marital status, education, smoking status, alcohol use, past medical treatment, past treatment, histology, and stage.

Comparison of Mean MCS Score

Results for the mean MCS score analysis are shown in **Table 1**. As participant's age increased, their MCS score increased and the oldest age group reported a statistically significant higher mean MCS score (70+: 47.5, $P<0.001$) compared to the youngest age group (<50: 45.4), indicating their perception of their mental QOL was better than the youngest age group. MCS scores for patients who had a high school, vocational, or associates degrees (45.8, $P<0.001$) or a college degree (47.6, $P<0.001$) were higher compared to those who did not finish high school (42.6, $P_{\text{trend}}=7.1\times10^{-24}$). Asian/Pacific Islanders (48.3, $P=0.034$) reported higher mean MCS scores compared to Whites (46.0). The lowest MCS score for alcohol usage was seen with former alcohol drinkers (44.5, $P=0.033$) and was significantly worse compared to never drinkers (45.5). Interestingly, current drinkers (47.1, $P<0.001$) reported a significantly higher MCS score compared to never drinkers. In addition, a downward trend of mean MCS scores was seen for former (46.1, $P<0.001$) and current (43.6, $P<0.001$) smokers compared to never smokers (48.0, $P_{\text{trend}}=5.4\times10^{-21}$). Divorced patients were more likely to have a worse mean MCS scores (44.1, $P<0.001$) compared to currently married patients (46.3). When examining histology type, patients with small cell lung cancer had the lowest MCS score (43.8, $P<0.001$) compared to those with adenocarcinoma (46.6). When stratifying by smoking, this relationship was only seen in ever smokers (data not shown). Finally, stage III (46.3, $P<0.001$) or IV (45.2, $P<0.001$) patients reported worse MCS scores compared to those with stage I (49.3) lung cancer.

Poor MCS Risk

The results for the adjusted risk analysis are shown in **Figure 3** and **Appendix: Supplemental Table 2**. Females were 41% ($\text{OR}=1.41$, 95% CI: 1.26-1.59, $P=6.8\times10^{-9}$) more likely to report a worse MCS when compared to males. Education was significantly associated with risk of reporting a poor MCS. Participants with a college degree had a lower risk of reporting a low MCS compared to patients with less than a high school education ($\text{OR}=0.50$, 95% CI: 0.41-0.61, $P=1.8\times10^{-11}$). Asian/Pacific Islanders were more likely to report a better

MCS (OR=0.72, 95% CI: 0.54-0.98, P=0.035) compared to Whites. When compared to never smokers, former smokers had a higher risk of reporting a poor MCS (OR=1.40, 95% CI: 1.19-1.65, P=3.8x10⁻⁵). Current smokers (when compared to never smokers) had an even bigger increased risk of reporting a poor MCS (OR=1.69, 95% CI: 1.38-2.06, P=2.9x10⁻⁷). Finally, patients diagnosed with stage IV lung cancer have a 75% (OR=1.76, 95% CI: 1.43-2.16, P=6.2x10⁻⁸) greater risk of reporting a worse MCS score compared to those diagnosed with stage I. As seen with PCS also, the stage IV lung cancer patients had the largest increased risk of poor MCS of all determinants examined in the model

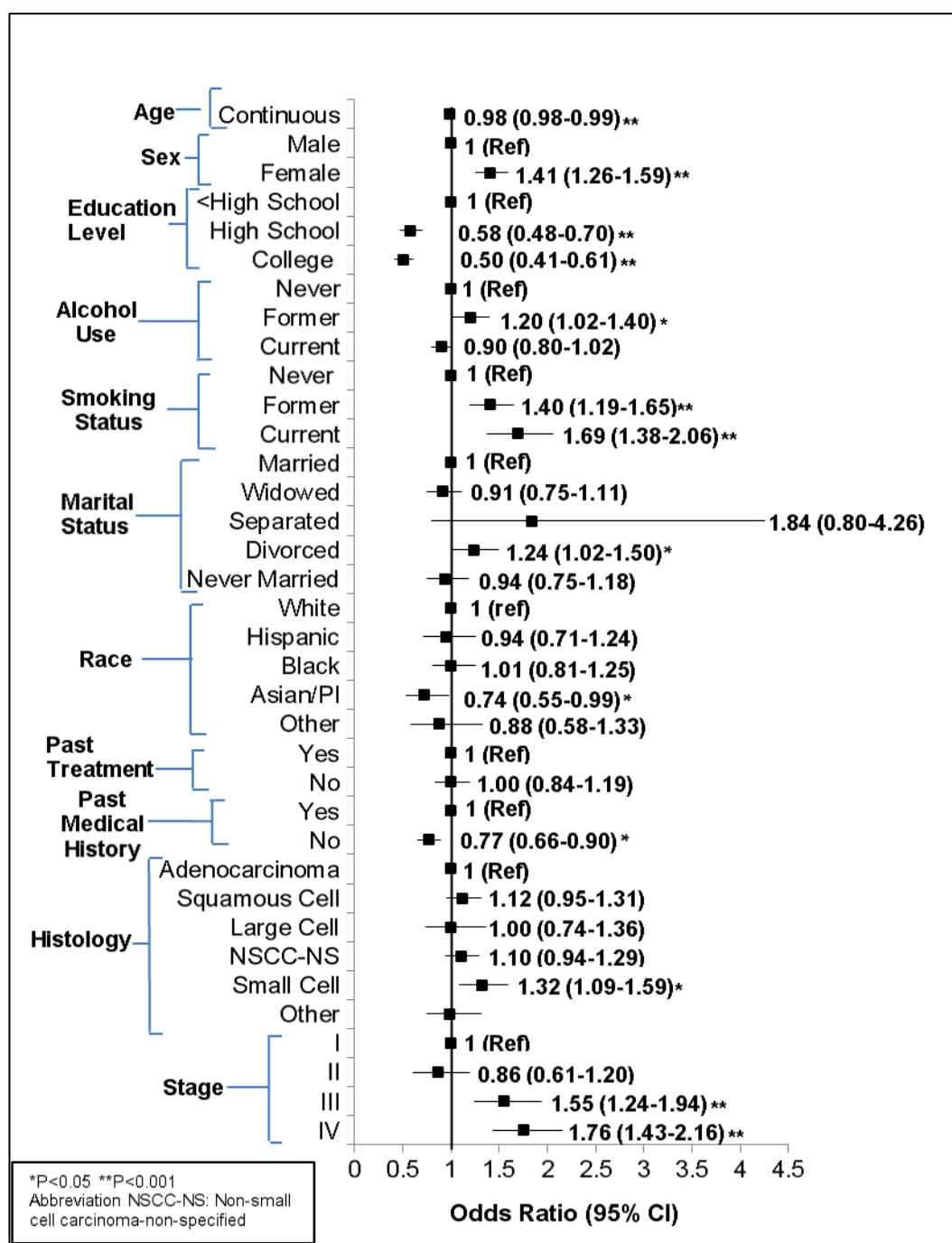


Figure 3. Association between demographic/clinical factors and MCS in lung cancer patients

Odds ratios adjusted by age, sex, race, marital status, education, smoking status, alcohol use, past medical treatment, past treatment, histology, and stage.

2.3.3. Relationship between PCS/MCS Scores and Survival

Survival analysis results based on dichotomized PCS and MCS scores are presented in **Table 3**. Individuals with a PCS or MCS score less than 50, had an increased risk of death (PCS: HR=1.63, 95% CI: 1.51-1.77, $P<1.0\times10^{-63}$; MCS: HR=1.23, 95% CI: 1.16-1.32, $P=7.2\times10^{-11}$). This increased risk resulted in a significant difference between median survival time (MST) of those with a PCS score less than 50 (MST=15.1 months) and those with a PCS score greater than 50 (MST=32.1 months, $P_{\log\text{-rank}}<0.0001$) (**Figure 4A**). There was also a significant reduction in MST for patients with a MCS score less than 50 at only 15.4 months and those with a MCS greater than 50 at 21.7 months ($P_{\log\text{-rank}}<0.0001$) (**Figure 4B**). When stratifying by stage, the same effect is seen within the stage groupings (**Figure 4C and 4D**).

Table 3. Association between Low PCS/MCS Score and Five-Year Overall Survival

SF-12 Score	Alive	Dead	Unadjusted HR (95% CI)	P Value	Adjusted HR (95% CI)	P Value
<u>PCS</u>						
High	645	852	1.00 (Ref)		1.00 (Ref)	
Low	1,344	3,579	1.91 (1.77-2.06)	$<1.0\times10^{-63}$	1.63 (1.51-1.77)	$<1.0\times10^{-63}$
<u>MCS</u>						
High	956	1,787	1.00 (Ref)		1.00 (Ref)	
Low	1,033	2,644	1.34 (1.26-1.43)	$<1.0\times10^{-63}$	1.23 (1.16-1.32)	7.2×10^{-63}

Abbreviations: HR=Hazard Ratio, CI-Confidence Interval

*Adjusted for age, sex, race, smoking status, previous cancer treatment, treatment at MD Anderson, histology, and cancer stage

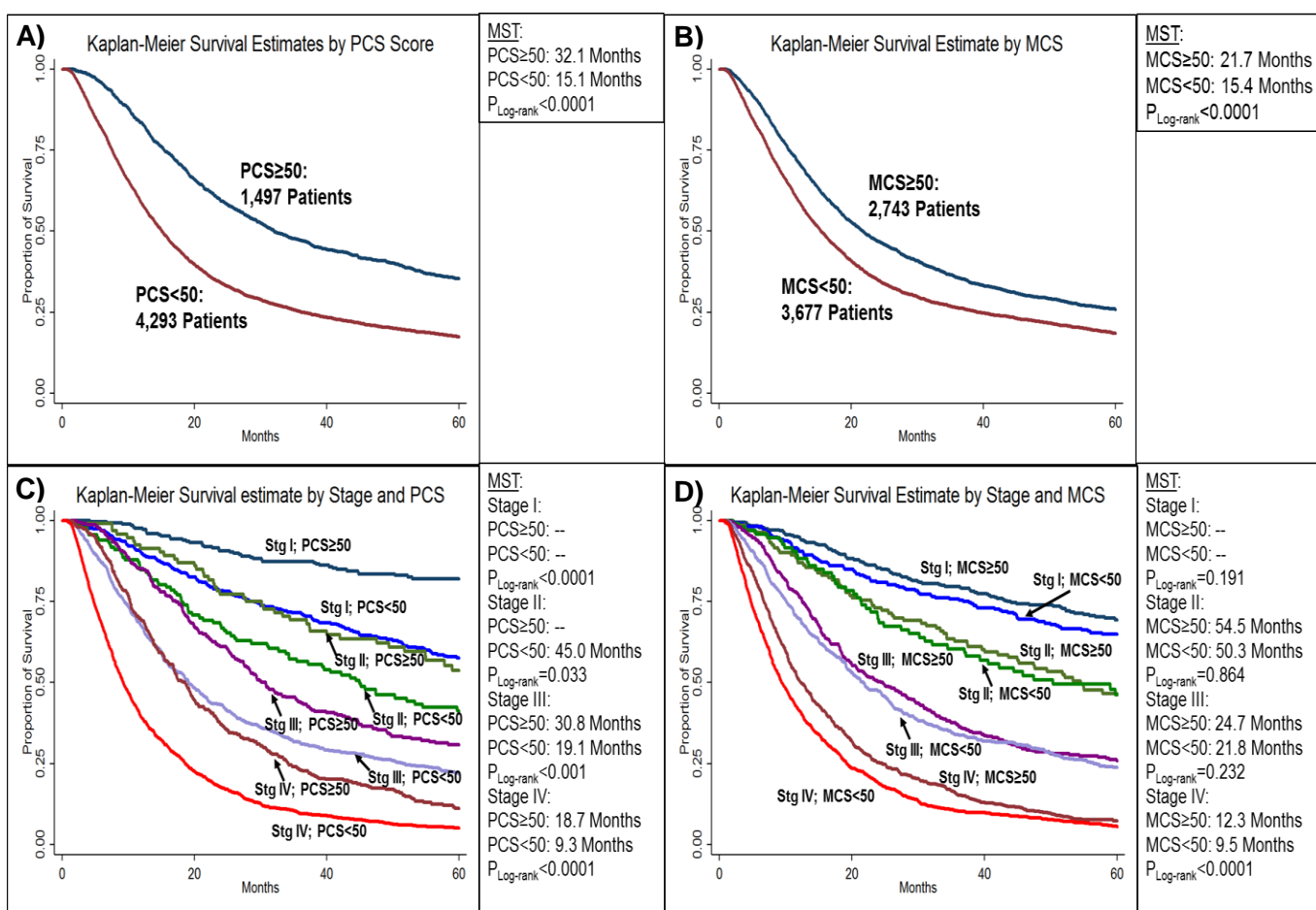


Figure 4. 5-year survival by quality of life measures in lung cancer patients and cancer

stage; A) PCS scores B) MCS scores C) PCS Score by Stage D) MCS Score by Stage

Scores were dichotomized at 50 representing the mean PCS/MCS score in the general population and stratified by cancer stage.

2.3.4. The Relationship between Genetic Variants in the p38 MAPK Pathway and PCS/MCS Scores

Discovery Phase for PCS and MCS Scores

The association between genetic variants in the p38 MAPK pathway and PCS/MCS scores are shown in **Appendix: Supplemental Table 3**. Overall, 29 SNPs were associated with PCS score and 20 SNPs were associated with MCS score in the discovery analysis. The most significant genetic variant associated with PCS score was *TNFRSF1B*: rs496888, which was associated with a higher PCS score (OR=0.40, 95% CI: 0.21-0.75, P=0.004) under the dominant model. The most significant variant associated with MCS score was located in *MAP2K3* (rs1466314) under the dominant model, with patients showing an over 2-fold increased risk of a poor MCS score (OR: 2.25, 95% CI: 1.31-3.87, P=0.003).

Gene-base Analysis for PCS and MCS Scores

When analyzing the gene-based analysis results from the VEGAS software, many genes were significant contributors to PCS and MCS scores in the discovery phase (data not shown). For PCS score this included *MAPK11* (P=0.011) and *PEX7* (P=0.005). For MCS score, this included *MAP2K3* (P=0.002) and *TRAF2* (P=0.023).

Validation Phase for PCS and MCS Scores

The validation phase results for MCS scores are seen in **Table 4**. No variants replicated when analyzing PCS score. One variant was replicated when analyzing variants and MCS score. In the discovery phase, individuals with homozygous variant genotype of *MEF2B*: rs2040562 showed a 3.06-fold increased risk of a poor mental health score (95% CI: 1.05-8.92, P=0.041), compared to subjects carrying at least one major allele. In the validation phase, individuals with homozygous variant genotype of *MEF2B*: rs2040562 showed a 2.61-fold increased risk of a poor MCS score (95% CI: 1.11-6.15, P=0.028) (when we combined discovery and validation phase: OR=2.43, 95% CI: 1.29-4.58, P=0.006 for rare homozygote genotype). When analyzing the gene-based analysis results, *MAP2K6* was a significant

contributor to PCS score based on the discovery phase p-values ($P=0.022$) and the validation phase p-values ($P=0.001$) (data not shown).

2.3.5. Relationship between Genetic Variants and Five-Year Survival

Appendix: Supplemental Table 4 provides the discovery phase of the association of genetic variants in the p38 MAPK pathway and five-year survival. Eighteen SNPs were significant. The most significant result was under the dominant model for *MAP3K5*: rs3765259. Patients with this variant had a decreased risk of dying ($HR=0.56$, 95% CI: 0.40-0.79, $P=0.0008$). Those with the common genotype had a MST of 17.3 months, those with one variant allele had a MST of 23.8 months ($P_{\log\text{-rank}}=0.053$). No variants that were significant in the discovery phase replicated.

Table 4. Association Between p38 MAPK Validated Variant and MCS Score

Discovery Phase					
Gene: SNP	Model	MCS <50 WW/WV/VV	MCS≥50 WW/WV/VV	*OR (95% CI)	P Value
<i>MEF2B</i> : rs2040562	Rec.	86/60/23	75/70/7	3.06 (1.05-8.92)	0.041
Validation Phase					
Gene: SNP	Model	MCS <50 WW/WV/VV	MCS≥50 WW/WV/VV	*OR (95% CI)	P Value
<i>MEF2B</i> : rs2040562	Rec.	62/76/28	56/84/14	2.61 (1.11-6.15)	0.028
Combined Analysis					
Gene: SNP	Model	MCS <50 WW/WV/VV	MCS≥50 WW/WV/VV	*OR (95% CI)	P Value
<i>MEF2B</i> : rs2040562	Rec.	148/136/51	131/154/21	2.43 (1.29-4.58)	0.006

Abbreviations: OR-Odds Ratio, Rec.-Recessive

*Adjusted for age, sex, marital status, education, smoking, alcohol, past medical treatment, previous treatment, histology, and stage

2.4. Discussion

To date there have been no studies reported that examine the association of detailed demographic and clinical characteristics and QOL in lung cancer patients. Furthermore, no study to date has examined the association of p38 MAPK genetic variants and QOL and survival. The results of this comprehensive study characterize the baseline demographic, epidemiological, clinical and genetic determinants of QOL in a large population of recently diagnosed lung cancer patients. Alcohol use, smoking, education, and higher lung cancer stage were consistently shown to impact mean PCS and MCS. Poor PCS and MCS QOL scores were associated with increased risk of death. Genetic variants in the p38 MAPK pathway were associated with PCS/MCS scoring. A validated SNP (*MEF2B*: rs2040562) was associated with an increased risk of poor MCS score.

The link between smoking and risk of lung cancer is well established. For our study, there were 1,197 current and 4,083 former smokers. Previous research has found that the majority of smokers who are current smokers when diagnosed with lung cancer will continue to smoke regardless of their cancer diagnosis(140). In our study, former and current smokers reported worse PCS and MCS scores compared to never smokers, and poor QOL in current smokers is consistent with the literature(128, 129). For example, one study that examined QOL and smoking status in SCLC patients with a positive smoking history found that patients that quit a year or more before their diagnosis reported better QOL scores compared to patients that quit within one year of their diagnosis or were still smoking at the time of their diagnosis(128). This is in line with our results in that current smokers reported lower PCS and MCS QOL scores than former smokers. Another study that grouped patients based on how their smoking status changed from diagnosis to one-year post diagnosis found that never smokers reported the best QOL, followed by former smokers, abstinent smokers (patients who quit between lung cancer diagnosis and one-year follow-up), and persistent smokers (patients who smoked at diagnosis and continued to smoke one-year follow-up)(129). In our study, former smokers reported slightly higher PCS and MCS scores than current smokers. This suggests that even

participants who are former smokers do not feel that their QOL is as high as never smokers, but does suggest that quitting smoking may lead to improved QOL. This presents the possibility of future smoking cessation programs in lung cancer survivors to assist current smokers in becoming former smokers with the goal of increasing their QOL and thus, potentially improving long-term prognosis.

Current alcohol users reported higher mean PCS and MCS scores than never drinkers and former drinkers. A previous study examining health perceptions in lung cancer survivors (5 to 21 years post diagnosis) found that approximately 69% of participants retrospectively self-reported that they were current drinkers when they were diagnosed with lung cancer and 57% of participants were still currently drinking(141). Those that were currently drinking were at a higher risk of reporting worse perception of health status(141). Interestingly, we found the opposite finding in our analysis for physical QOL in recently diagnosed lung cancer cases. Our analysis is the first to our knowledge that has examined alcohol use and QOL in newly diagnosed lung cancer cases. Further analysis is warranted to dissect the potentially complicated relationship between alcohol use and QOL.

Previous research has shown that healthy individuals with lower education levels report worse QOL and therefore are diagnosed with chronic diseases more frequently compared to those with more favorable QOL(142-144). There is limited research on the association between education level and QOL in lung cancer patients. The few studies on lung cancer found that lower education level is associated with poorer performance status in clinical trial participants(145, 146) and higher education is associated with better QOL and lower symptom levels(147). Mixed results have been seen between education level and different aspects of QOL in NSCLC patients (148) and survivors (149). Specifically, lower educated survivors of NSCLC (treated by surgery) displayed better cognitive functioning compared to individuals with a higher education level but they also reported worse pain and financial related stress(149). Cognitive functioning, pain, stress, and symptoms are variables that affect QOL. Our study is first to examine education level and QOL in a large population of newly diagnosed patients and

we showed that patients with at high school degree or higher were more likely to report higher PCS and MCS scores. Further research is needed to determine possible disparities feeding into the gap between QOL and education level in patients.

The p38 MAPK pathway has been associated with QOL and QOL factors such as depression, pain, and there is evidence of an association with anxiety in animal models(112, 150, 151). Individuals diagnosed with major depression have increased levels of proinflammatory cytokines and corresponding receptors in peripheral blood and cerebral spinal fluid(112, 152), and proinflammatory cytokines activate the p38 MAPK pathway, which subsequently and can activate the serotonin transporter (SERT)(153). Furthermore, research has linked the activation of the p38 MAPK pathway to regulation of mood-related neurotransmitters, with potential links to the regulation of synaptic plasticity(154). Our study discovered multiple variants in p38 MAPK pathway genes that were associated with PCS and MCS scores. One variant (*MEF2B*: rs2040562) was replicated in association with mental QOL. Myocyte-enhancing factor 2B (MEF2B) protein is a transcription factor that is important in development and adulthood and is important in regulating transcriptional programming(155). The variant rs2040562, that validated, is intronic. Research has shown that patients with metastatic renal cell carcinoma who are depressed (compared to non-depressed patients) show increased expression of *MEF2*(156). Our results suggest that individuals with a variant in *MEF2B* are at an increased risk of reporting a poor MCS score. Therefore, further research needs to be completed to untangle the mechanism behind this relationship.

Finally, we identified that individuals with poor reported PCS or MCS scores are at a higher risk for death within five-years of diagnosis and our results support and extend previous findings(157-161) that examined QOL during or following treatment. We examined QOL at baseline and studies that examined baseline QOL and survival in lung cancer patients support our findings(25, 118, 120, 121, 123, 162-165). Our findings remained true after controlling for stage and treatment. Previous studies have shown this relationship in patients with Stage I NSCLC that received pulmonary resection(161), further providing evidence that QOL is an

important prognostic indicator even in early stage patients. Our patient population was unique in that it was heterogeneous in terms of consisting of multiple types of lung cancer. The majority of studies examining QOL and survival in lung cancer patients focus on NSCLC. For example, one study examining 1,194 NSCLC patients found that overall QOL and physical functioning were independently associated with survival in a multivariate analysis controlling for stage and other confounders(123). One study did examine baseline QOL and survival in a small sample of mixed histology's. They found that pre-diagnosis QOL (in patients suspected to have lung cancer) was associated with survival. Specifically, those that reported better QOL were less likely to die(118). These results further highlight that many factors influence survival and stress the importance of potential behavioral interventions in the clinical setting to increase QOL and potentially improve survival.

Because of the significant association between QOL and survival that has been shown in many studies, an effort should be made to implement this in the clinic. According to researchers, a barrier to clinical use isn't the lack of valid measures of QOL, it is the difficult nature of implementing QOL into busy clinic schedules(165, 166). In contrast, because QOL is becoming a recognized aspect of cancer care, QOL has become an important endpoint of clinical trials(166).

The strengths of this study include a large study population and the ability to assess the relationship of various demographic, epidemiological, clinical, and genetic factors with QOL. The results of this study are important in that they provide an overarching picture of key QOL factors that affect lung cancer patients. This information could be used to identify potential interventions to improve QOL, as well as those at increased risk of a poor treatment response and prognosis due to their reduced QOL. The main limitation of this study is that over 2,800 patients were missing stage information. The results of a sensitivity analysis showed consistency between the full model and the reduced model.

In conclusion, we have identified several determinants that contribute to and mediate QOL in lung cancer patients. The results of this study can be used to identify patients that may have

a worse QOL and are at risk for a poor prognosis. This could result in more of a proactive approach in the clinic to treating the patient as a whole, identifying genetically susceptible patients, and addressing health behaviors that impact QOL, such as smoking cessation as a step to improve patient well-being and overall survival.

Chapter 3. Quality of Life, its Socio-Demographic and Racial Determinants, and Clinical Outcomes among Breast Cancer Patients

3.1. Introduction

Breast cancer is the number one diagnosed cancer and the number two cause of cancer related death in women in U.S.(1). Breast cancer is a heterogeneous disease and is often classified in three receptor subtypes: Hormone-receptor positive (HmR-positive), human epidermal growth factor 2 positive (HER2-positive), and triple-negative(58, 167). The receptor subtypes of breast cancer are important in regards to optimal treatment options and prognosis of disease(168). Triple-negative breast cancer is the most aggressive of the three major subtypes and is found in higher rates in Black women and younger pre-menopausal women(140, 169).

QOL is a multidimensional concept that spans the psychological, physical, financial, and spiritual aspects of a person's life(170). QOL has become an important part of a cancer patient's treatment plan due to the association of better survival in patients with better QOL, including breast cancer patients(119, 171). Breast cancer patients can have many different QOL concerns to deal with. Physical QOL issues such as fatigue, pain, nausea are common in women with breast cancer(170). Research supports that there are racial disparities when measuring QOL in breast cancer patients. For example, Hispanic women have been shown to report worse mental, physical, and social QOL compared to other race groups(172). African Americans report low QOL in some domains and high QOL in other domains. In one study, African Americans reported lower functional well-being and higher emotional well-being compared to White women(96). Many studies that examined racial disparities of QOL in breast cancer patients focused on these issues in long-term breast cancer survivors(173-176) but not on recently diagnosed patients. Furthermore, the studies that did examine QOL at diagnosis are plagued by small sample sizes. Currently, there lacks a comprehensive study that examines predictors of QOL at diagnosis and how predictors vary across racial groups.

Racial disparities exist for survival time for many types of cancer(60). When examining racial disparities in breast cancer specifically, Black women actually have slightly lower incidence rates of breast cancer compared to White women(60). While Black women have a

lower incidence of breast cancer, they are typically diagnosed with later stage disease, are at a higher risk for recurrence, and have the worst survival(60, 177, 178). Black women also have the worst survival for each known stage of disease at diagnosis(30, 60) while Asian/PI patients have the highest survival(60). Some reasons for the disparity in Black women are known. For example, lack of access to care and inferior treatment are all considered important factors(179), but that is thought to only contribute partially to the disparity in mortality. Another potential reason for the disparity in survival is due to the fact that African Americans are more likely to be diagnosed with more aggressive molecular subtypes like triple-negative which have poorer outcomes(41). In addition, Hispanics also show worse survival compared to Whites and this may be due to receiving inferior care(180). Another potential factor that could contribute to racial disparities in survival of breast cancer is health-related QOL(181).

In this current study, we aim to establish the association between QOL and clinical outcomes using a large population from The University of Texas MD Anderson Cancer Center. We also aim to discover the host and clinical predictors of QOL in newly diagnosed breast cancer patients, and how these determinants vary in distribution across race groups, with the ultimate goal being to characterize host and clinical characteristics among racial groups.

3.2. Methods

3.2.1. Patient Population

Patients for this study were obtained from The University of Texas MD Anderson Cancer Center from 2002 to 2011. There were 10,681 women newly diagnosed with Stage I through III breast cancer that were diagnosed within one year of enrollment. Patients completed an institutional intake questionnaire within one year of their diagnosis. All patients completed written informed consent and this study was approved by The University of Texas MD Anderson Cancer Center Institutional Review Board.

3.2.2. Data Collection

Epidemiologic Data

The institutional intake questionnaire asked epidemiologic questions. These included questions regarding self-reported race, age, smoking history, alcohol history, past medical history, marital status, and education level. Race/Ethnicity was classified as “White”, “Hispanic”, “Black”, “Asian/PI”, “Other”. Alcohol consumption and smoking status was classified into three groups: “Never”, “Former”, and “Current”. Patients were classified as a “current” drinker if they drank at least one drink per month. BMI was measured at time of first clinic appointment. Patients were asked to self-report if they had ever had any of the following past medical history events: Diabetes, stroke, heart or lung problems, high blood pressure, bleeding problems, liver problems, thyroid problems, frequent infections, kidney problems, HIV/AIDS, psychiatric or psychological issues, seizures, or circulation issues. Clinical data was abstracted from electronic medical records by trained staff. Pathology data, survival data, and treatment information was obtained from MD Anderson’s Tumor Registry.

Quality of Life

A QOL questionnaire (SF-12v1) was included in the institutional intake questionnaire that patients completed. The SF-12v1 is a validated QOL measure(89) that measures patient’s physical and mental QOL by calculating a physical component summary score (PCS) and mental component summary score (MCS)(89). The 12 questions in the questionnaire referred

to the previous four weeks. Eight subscales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) were calculated from the responses which are used to formulate the PCS and MCS. The PCS and MCS score were normalized to a mean of 50 (SD=10) based on the US general population. A higher score indicates a better QOL. The pain question in the SF-12v1 that asked “During the past 4 weeks, how much did pain interfere with your normal work” was modified and scoring was adjusted to match the SF-12v1 scoring in our patient intake questionnaire as “During the past week, has pain interfered with your general activities”.

3.2.3. Statistical Analysis

To analyze the association between QOL and overall survival and recurrence in breast cancer patients, Cox proportional hazard regression was used to calculate hazard ratios (HRs), 95% confidence intervals (95% CI), and p-values. Patients that died or who were alive at last follow-up without recurrence were censored. Recurrence was either local, regional, or distant metastatic recurrence and time to recurrence was defined from the date of diagnosis to the date of first recurrence, date of last follow-up, or date of death, whichever came first. Survival time was calculated from date of diagnosis to the date of death or the date of last follow-up, whichever came first. PCS and MCS were grouped into five score groups starting at 40 and increasing by half standard deviation (a score increase of 5), to understand how survival and recurrence may differ as PCS and MCS score changes. The recurrence model was adjusted for age, race, diagnosis year, cancer detection method, nuclear grade, histology, tumor size, number of positive lymph nodes, lymphatic/vascular invasion, adjuvant hormone therapy, alcohol use, receptor subtype, and stage. Survival model was adjusted for age, race, cancer detection method, nuclear grade, tumor size, number of positive lymph nodes, lymphatic/vascular invasion, chemotherapy, adjuvant hormone therapy, receptor subtype, smoking, and stage. These factors were based on a previous prognostic model study that investigated a comprehensive list of potential predictors including receptor subtypes, epidemiological data, QOL, and treatment data and these factors were found to be significant

predictors(58). Kaplan-Meier curves were generated to assess the survival and recurrence differences among races and among PCS and MCS scores. Log-rank tests were performed to assess differences in survival and recurrence by race and QOL score. A subset of the study population had detailed clinical data. To test for differences in mean PCS and MCS scores among host and clinical characteristics, an ANOVA test was used and SIDAK was used to correct multiple comparisons. Adjusted linear regression was completed for clinical factors using the clinical subset population to provide adjusted p values for multiple comparison testing (adjusting for age, race, education, BMI, marital status, smoking, alcohol use, past medical history score, stage, previous treatment, cancer detection method, nuclear grade, lymphatic/vascular invasion, tumors size, number of positive lymph nodes, breast cancer receptor status, histology, year diagnosed, and menopause status).

3.3. Results

3.3.1. Host Characteristics

Table 5 shows the host characteristics of the study population. The majority of patients were between the ages of 45 and 54 years. Approximately 70% of the study population was White, followed by similar numbers of Hispanics and Blacks and only 4.9% of the population was Asian/PI. Over 4,500 (46.7%) women had at least a college degree and over 6,500 (65.1%) women were never smokers. Of the three BMI categories, 36.8% of women fell in to the normal/underweight BMI category (BMI<25). For a subset of the study population we had extensive clinical data (N=6,807). When examining clinical characteristics, most women in this study were diagnosed with HmR-positive receptor subtype (N=4,434), and 3,231 women detected their cancer by screening and 3,526 women detected their cancer by symptoms. Distributions of epidemiologic factors were similar between the full population and the subset of clinical population (**Table 6**) indicating the two populations were similar.

Table 5. Study Host and Clinical Characteristics

Epidemiology Characteristics		N	%	Clinical Characteristics*		N	%
Age	18-44	2,620	25.7	Breast Cancer Receptor Subtype			
	45-54	3,399	33.3	HmR-Positive			
	55-64	2,571	25.2	HER2-Positive			
	≥65	1,607	15.8	Triple-Negative			
				Adjuvant Hormone Therapy			
Race	White	7,002	70.5	Yes			
	Hispanic	1,186	11.9	No			
	Black	1,021	10.3	Chemotherapy			
	Asian/PI	490	4.9	Yes			
	Other	237	2.4	No			
Education Level	High School or Less	2,516	25.8	Cancer Detection Mode			
	AA/Voc	2,685	27.5	Screening			
	College Degree or Greater	4,548	46.7	Symptoms			
Marital Status	Married	7,210	70.8	Nuclear Grade			
	Never Married	1,214	11.9	I or II			
	Other	1,765	17.3	III			
Smoking	Never	6,566	65.1	Lymphatic or Vascular Invasion			
	Former	2,708	26.8	No			
	Current	820	8.1	Yes			
				Tumor Size			
Alcohol	Never	4,897	48.6	0-1 cm			
	Former	757	7.5	1-2 cm			
	Current	4,418	43.9	≥3			
BMI	<25	2,412	36.8	Diagnosis Year			
	25-29.9	1,962	30.0	1999-2002			
	≥30	2,175	33.2	2003-2007			
Past Medical History Score	0	2,952	29.0	2008-2012			
	1	3,063	30.0	Menopause			
	2	2,180	21.4	Premenopause			
	≥3	2,002	19.6	Perimenopause			
				Postmenopause			
Previous Treatment	Yes	4,321	42.4	Positive Lymph Nodes			
	No	5,876	57.6	0			
				1 or 2			
				≥3			
				Histology			
Stage	I	1,517	14.9	Ductal			
	II	2,071	20.3	Lobular			
	III	890	8.7	Mixed Ductal/Lobular			
	Unknown	5,719	56.1	Other			

*Clinical data only available for a subset (N=6,807) of patients

Table 6. Distribution of Host Characteristics in Subset Population

Epidemiology Factors	N	%
Age		
18-44	1,705	25.1
45-54	2,204	32.4
55-64	1,768	26.0
≥65	1,130	16.6
Race		
White	4,663	70.4
Hispanic	820	12.4
Black	665	10.0
Asian/PI	323	4.9
Other	154	2.3
Education Level		
High School or Less	1,766	27.1
AA/Voc	1,775	27.3
College Degree or Greater	2,967	45.6
Marital Status		
Married	4,784	70.3
Never Married	798	11.7
Other	1,219	17.9
Smoking		
Never	4,338	64.4
Former	1,847	27.4
Current	549	8.2
Alcohol		
Never	3,255	48.4
Former	505	7.5
Current	2,961	44.1
BMI		
<25	2,412	36.8
25-29.9	1,962	30.0
≥30	2,175	33.2
Previous Treatment		
No	4,070	59.8
Yes	2,737	40.2
Past Medical History Score		
0	1,948	28.6
1	2,039	30.0
2	1,473	21.6
≥3	1,347	19.8
Stage		
I	1,403	37.6
II	1,682	45.0
III	650	17.4

3.3.2. Predictors of Clinical Outcomes in Breast Cancer Patients

QOL and Overall Survival

The results showing the association between PCS/MCS and overall survival are shown in **Table 7**. Compared to patients with a PCS of 55 or greater, as PCS decreased by half a standard deviation (5 points), there was a dose-dependent increase in the risk of death with patients who reported a PCS score of less than 40 having the highest risk of death (HR=2.00, 95% CI: 1.64-2.43, $P=3.5 \times 10^{-12}$). **Figure 5A** shows the Kaplan-Meier curves assessing the difference in survival by PCS score ($P_{\text{Log-rank}} < 0.0001$). Patients with a PCS of less than 40 showed the worst survival, with a median survival time (MST) of 11.7 years, followed by patients with a PCS score of 40 through 44 (MST=12.5 years). When examining mental QOL and risk of death, there was no significant association between MCS score and risk of death in the adjusted regression model. **Figure 5C** shows the Kaplan-Meier curve of MCS score and survival ($P_{\text{Log-rank}} = 0.005$). We also analyzed PCS score and overall survival by stage (I-III). The trends were similar to the overall results (**Figure 6A** and **Figure 6B**).

QOL and Risk of Recurrence

Table 7 shows the results of the association between PCS/MCS and recurrence. Patients who scored 40-44 or <40 on the PCS had a significant 41% (HR=1.41, 95% CI: 1.05-1.91, $P=0.023$) or 42% (HR=1.42, 95% CI: 1.12-1.80, $P=0.003$) increase in the risk of recurrence, respectively. The difference in recurrence by PCS score is seen in **Figure 5D**. Patients with a PCS score of less than 40 showed the highest recurrence compared to the other PCS groups ($P_{\text{Log-rank}} < 0.0001$). For MCS score, there was no significant association with recurrence (**Table 7**). The results were stratified by stage and trends were similar to the overall results (**Figure 6C** and **Figure 6D**).

Table 7. The Association Between PCS/MCS and Survival and Recurrence

Score	Event	No Event	HR (95% CI)*	P Value
Survival				
PCS Score				
PCS≥55 (Ref)	208	2,161	1.00 (Ref)	
PCS 50-54	167	1,294	1.23 (1.00-1.51)	0.054
PCS 45-49	103	631	1.40 (1.10-1.78)	0.006
PCS 40-44	87	469	1.59 (1.23-2.05)	4.6x10 ⁻⁴
PCS<40	266	932	2.00 (1.64-2.43)	3.5x10 ⁻¹²
Dichotomized PCS Score				
≥50	375	3,455	1.00 (Ref)	
<50	456	2,032	1.58 (1.36-1.82)	6.0x10 ⁻¹⁰
MCS Score				
MCS≥55 (Ref)	242	1,765	1.00 (Ref)	
MCS 50-54	148	1,045	1.05 (0.85-1.29)	0.664
MCS 45-49	105	848	0.95 (0.76-1.20)	0.687
MCS 40-44	114	601	1.16 (0.92-1.46)	0.210
MCS<40	222	1,228	1.07 (0.88-1.29)	0.510
Dichotomized MCS Score				
≥50	400	2,901	1.00 (Ref)	
<50	431	2,586	1.01 (0.87-1.16)	0.937
Recurrence				
PCS Score				
PCS≥55 (Ref)	205	2,325	1.00 (Ref)	
PCS 50-54	151	1,401	1.19 (0.94-1.50)	0.141
PCS 45-49	80	710	1.14 (0.85-1.51)	0.381
PCS 40-44	80	522	1.49 (1.10-2.00)	0.009
PCS<40	201	1,073	1.45 (1.14-1.83)	0.002
Dichotomized PCS Score				
≥50	356	3,726	1.00 (Ref)	
<50	361	2,305	1.26 (1.06-1.49)	0.009
MCS Score				
MCS≥55 (Ref)	203	1,940	1.00 (Ref)	
MCS 50-54	128	1,139	0.99 (0.77-1.26)	0.915
MCS 45-49	93	922	0.81 (0.62-1.07)	0.141
MCS 40-44	99	672	1.14 (0.87-1.49)	0.343
MCS<40	194	1,358	0.91 (0.73-1.14)	0.422
Dichotomized MCS Score				
≥50	344	3,174	1.00 (Ref)	
<50	373	2,857	0.92 (0.78-1.08)	0.295

*Adjusted for host and clinical factors

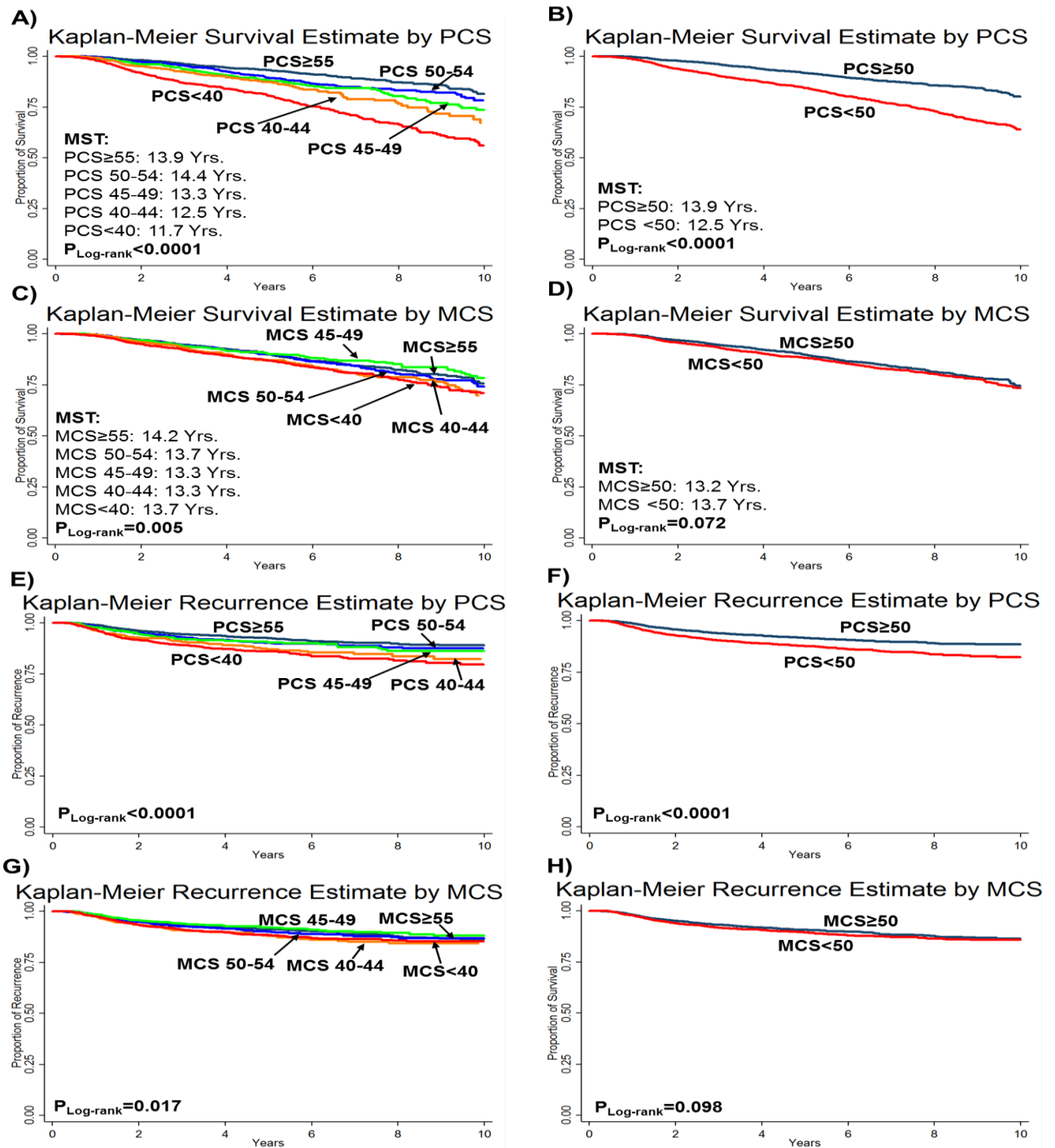


Figure 5. The Association between quality of life measures and clinical outcomes in the breast cancer study population; A) PCS and survival B) PCS dichotomized by 50 and survival C) MCS and survival D) MCS dichotomized by 50 and survival E) PCS and Recurrence F) PCS dichotomized by 50 and recurrence G) MCS and recurrence H) MCS dichotomized by 50 and recurrence

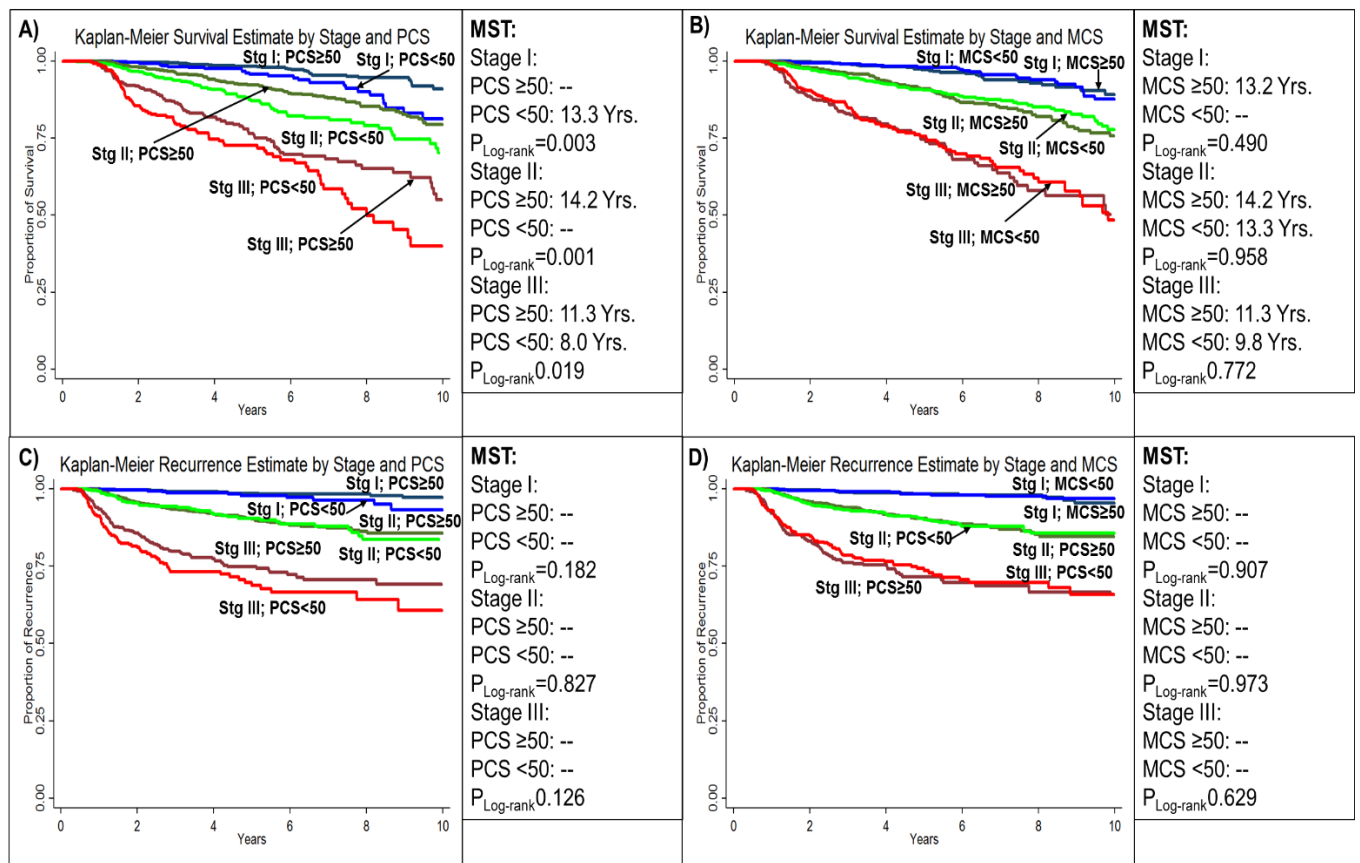


Figure 6. The Association between quality of life measures and clinical outcomes in the breast cancer study population by stage; A) PCS and survival B) MCS and Survival C) PCS and recurrence D) MCS and recurrence

3.3.3. Differences in Clinical Outcomes by Race

Figure 6A shows the Kaplan Meier curve for overall survival differences by race. Asian/PI patients showed the best survival compared to the other race groups. Black patients showed the worst survival compared to all other racial groups ($P_{\text{Log-rank}} < 0.0001$). **Figure 6B** showed the difference in recurrence between racial groups. Black patients showed the highest recurrence compared to other racial groups ($P_{\text{Log-rank}} < 0.0001$).

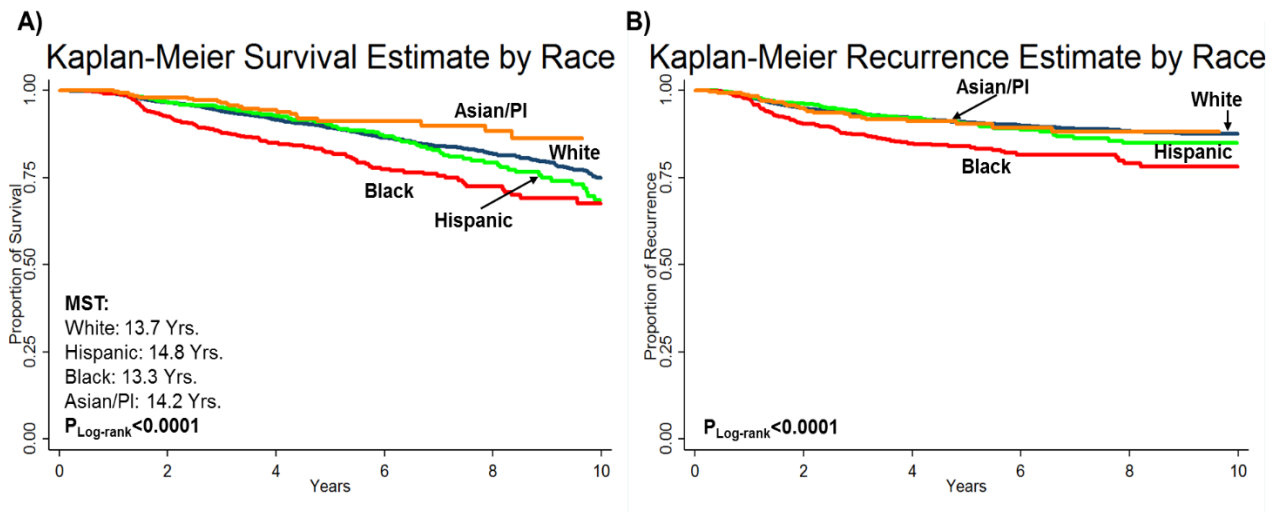


Figure 7. The association between race and clinical outcomes in breast cancer patients;

A) Race and overall survival B) Race and recurrence

3.3.4. QOL Distribution by Race

PCS

Next, the distribution of PCS score was analyzed by race (**Figure 7A**). Asian/PI showed the highest percentage of patients with a PCS score of greater than or equal to 50 (64%), indicating a good QOL. Asian/PI also had the lowest percentage (32%) of patients who reported a PCS of less than 30 (two standard deviations below the US mean of 50). In contrast, Black patients had the highest percentage of patients that reported a PCS of less than 30 (12%), and the lowest percentage of patients that reported a PCS of 50 or greater (50%). Hispanics had the next lowest percentage of patients who reported a PCS of 50 or greater (58%).

MCS

When analyzing the distribution of MCS score by race (**Figure 7B**), Black breast cancer patients had the highest percentage (54%) of participants who scored 50 or greater, indicating a good QOL. Hispanic patients had the highest proportion (9%) of patients who had a MCS score of less than 30, with Asian/PI, White, and Black groups all having 7% of patients who scored less than 30. Hispanics also had the lowest percentage of patients that scored a MCS score of 50 or greater, meaning they had the lowest proportion of patients with good mental QOL.

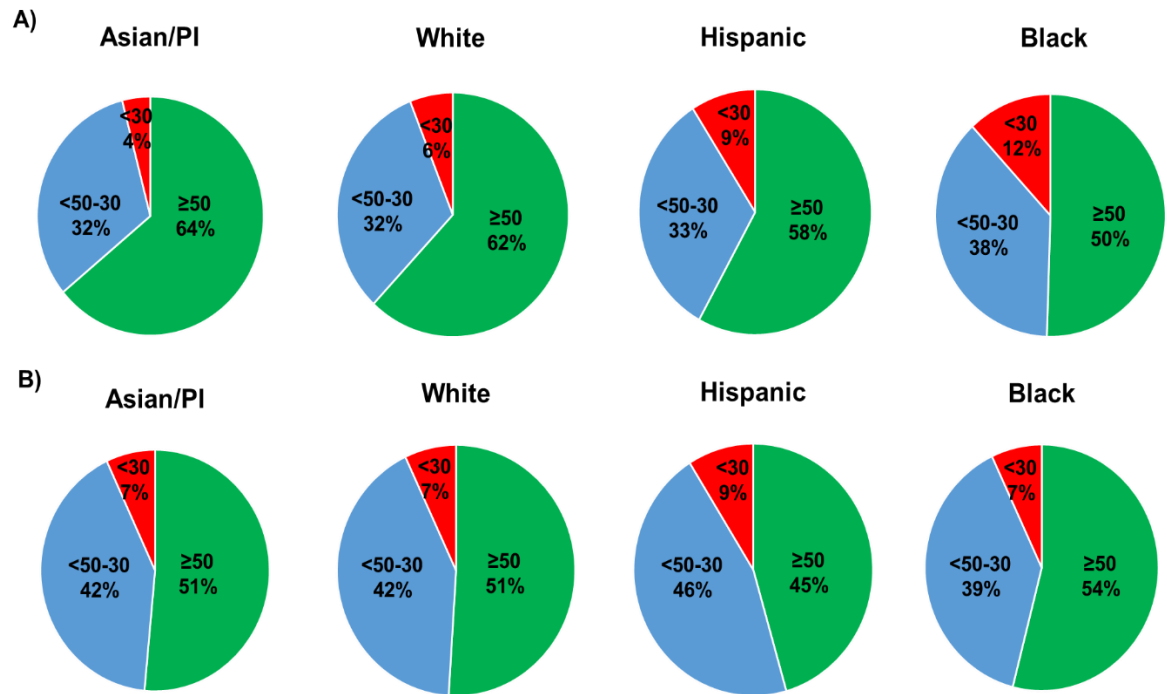


Figure 8. Distribution of quality of life measures among Race; A) Distribution of PCS B)

Distribution of MCS

Grouped by Scores of <30, 30-50, and ≥50.

3.3.5. Determinants of QOL

PCS

Table 8 shows the results of how PCS score differs among different host and clinical factors. For the host characteristics, BMI was inversely associated with PCS with patients who had a BMI of 30 or greater (PCS=46.5) reporting a 5 point lower PCS score compared to patients with a BMI of <25 (PCS=51.6, $P=1.1 \times 10^{-20}$). Hispanic and Black patients were more likely to report lower PCS scores (PCS=47.9 $P=0.005$, PCS=46.4 $P=0.008$, respectively) compared to White patients (PCS=49.4). College educated or post graduate educated patients reported higher PCS scores (PCS=50.7) compared to patients with a high school education or less ($P=46.9$, $P=1.6 \times 10^{-6}$). When examining clinical characteristics, breast cancer patients who discovered their cancer by regular screening methods reported higher PCS scores (PCS=49.4) than patients who discovered their cancer based on symptoms (PCS=48.8, $P=6.7 \times 10^{-4}$). Triple-negative patients reported on average a 2 point lower PCS score (PCS=47.5, $P<0.001$) compared to patients with HmR-positive cancer (PCS=49.4), which was not significant in the adjusted analysis. Perimenopausal women reported higher PCS (PCS=50.7, $P=0.042$) scores compared to premenopausal women (PCS=48.0).

Table 8. Demographic and Clinical Predictors of PCS

Characteristic	N	Mean PCS (SD)	P Value	P Value*	Clinical Characteristic	N	Mean PCS (SD)	P Value	P Value*
Age					Cancer Detection Method				
18-44	2,260	50.2 (9.5)			Screening	3,231	49.4 (9.7)		
45-54	3,399	49.6 (9.8)	0.211	0.829	Symptoms	3,526	48.8 (10.1)	0.047	6.7x10 ⁻⁴
55-64	2,571	48.2 (10.6)	<0.001	0.704	Nuclear Grade				
≥65	1,607	46.4 (10.7)	<0.001	0.020	I or II	3,464	49.7 (9.6)		
P _{trend}			<0.001		III	3,210	48.5 (10.2)	<0.001	0.489
BMI					Lymphatic or Vascular Invasion				
<25	2412	51.6 (8.9)			No	5,097	49.4 (9.8)		
25-29	1962	49.4 (9.7)	<0.001	5.6x10 ⁻⁵	Yes	1,686	48.3 (10.4)	<0.001	0.136
≥30	2175	46.5 (10.4)	<0.001	1.1x10 ⁻²⁰	Tumor Size				
Race					0-1 cm	1,849	50.2 (9.5)		
White	7,002	49.4 (10.0)			1-2 cm	2,336	49.4 (9.7)	0.088	0.095
Hispanic	1,186	47.9 (10.6)	<0.001	0.005	≥3	2,247	47.8 (10.4)	<0.001	2.7x10 ⁻⁶
					Number of Positive Lymph Nodes				
Black	1,021	46.4 (10.8)	<0.001	0.008	0	3,737	49.8 (9.5)		
Asian/PI	490	50.0 (8.8)	0.938	0.084	1 or 2	1,587	49.1 (10.1)	0.109	0.013
Other	237	48.3 (10.5)	0.806	0.391	≥3	1,413	47.5 (10.6)	<0.001	6.7x10 ⁻⁴
Education					Receptor Subtype				
HS or Less	2,516	46.9 (10.8)			HmR-positive	4,434	49.4 (9.8)		
Voc./AA	2,685	48.0 (10.5)	0.001	0.715	HER2-positive	995	49.2 (10.0)	0.910	0.672
College	4,548	50.7 (9.3)	<0.001	1.6x10 ⁻⁶	Triple-negative	943	47.5 (10.6)	<0.001	0.101
Alcohol					Menopause				
Never	4,897	47.5 (10.7)			Premenopause	4,017	48.0 (10.3)		
Former	757	45.8 (11.1)	<0.001	0.021	Perimenopause	2,586	50.7 (9.2)	<0.001	0.042
Current	4,418	51.0 (8.9)	<0.001	5.4x10 ⁻¹²	Postmenopause	191	49.9 (10.1)	0.062	0.970
Smoking					Diagnosis Year				
Never	6,566	49.3 (9.9)			1999-2002	722	49.1 (10.3)		
Former	2,708	48.6 (10.3)	0.044	0.241	2003-2007	2,593	49.2 (9.8)	0.976	0.633
Current	820	46.9 (11.1)	<0.001	1.9x10 ⁻⁶	2008-2012	3,492	49.0 (9.9)	0.994	0.677
Marital Status					Histology				
Married	7,210	49.5 (9.8)			Ductal	5,421	49.0 (10.0)		
Never Married	1,214	47.9 (10.7)	<0.001	1.9x10 ⁻⁴	Lobular	584	50.0 (9.3)	0.136	0.111
Other	1,765	46.9 (11.0)	<0.001	0.038	Mixed				
Past Medical History Score					Ductal/Lobular	402	49.4 (10.0)	0.970	0.900
0	2,952	51.4 (8.5)			Other	400	48.4 (10.3)	0.719	0.753
1	3,063	50.1 (9.3)	<0.001	9.3x10 ⁻⁴					
2	2,180	48.5 (10.2)	<0.001	1.4x10 ⁻¹⁰					
≥3	2,002	43.8 (11.7)	<0.001	9.3x10 ⁻⁶³					
Previous Treatment									
None	5,876	50.9 (9.2)							
Yes	4,321	46.1 (10.8)	<0.001	9.0x10 ⁻²⁰					
Stage									
I	1,517	51.3 (9.0)							
II	2,071	51.2 (9.1)	1.000	6.8x10 ⁻⁵					
III	890	49.7 (9.9)	0.001	0.096					

*Adjusted

MCS

Table 9 shows the host and clinical characteristics analyzed to assess the difference in MCS scores among groups to better understand predictors of mental QOL. Patients who were 55 years of age and older (Age 55-64: MCS=48.6, $P=2.7 \times 10^{-10}$; Age ≥ 65 : MCS=50.8, $P=1.2 \times 10^{-23}$) reported significantly higher MCS scores compared to patients who were between the ages of 18 and 44 (MCS=46.2). Blacks showed a higher MCS score (MCS=48.4, $P=5.8 \times 10^{-5}$) compared to White patients (MCS=47.8). College educated/post graduate school (MCS=48.4, $P=1.1 \times 10^{-5}$) patients were more likely to report a higher MCS compared to patients who had a high school degree or less (MCS=47.3). Former (MCS=47.4, $P=0.002$) and current (MCS=43.7, $P=6.4 \times 10^{-11}$) smokers and former alcohol drinkers (MCS=45.3, $P=3.9 \times 10^{-6}$) reported, on average, lower MCS scores compared to never smokers (MCS=48.4) and never drinkers (MCS=48.2), respectively. When examining clinical characteristics and how MCS scores differ among groups, women who discovered their breast cancer based on symptoms scored lower mean MCS scores (MCS=46.9, $P=0.001$) compared to women who discovered their cancer by routine screening (MCS=48.6). Patients with a nuclear grade III tumor (MCS=47.1, $P<0.001$) and patients with lymphatic vascular invasion (MCS=47.0, $P=0.005$) reported lower MCS scores compared to patients with grade I or II tumors (MCS=48.3) or tumors with no lymphatic vascular invasion (MCS=48.0), but these associations were not significant in the adjusted analysis.

Table 9. Host and Clinical Predictors of MCS

Characteristic	N	Mean MCS (SD)	P Value	P Value*	Clinical Characteristic	N	Mean MCS (SD)	P Value	P Value*
Age					Cancer Detection Method				
18-44	2,260	46.2 (10.5)			Screening	3,231	48.6 (10.2)		
45-54	3,399	46.9 (10.4)	0.129	0.033	Symptoms	3,526	46.9 (10.7)	<0.001	0.001
55-64	2,571	48.6 (10.3)	<0.001	2.7×10^{-10}	Nuclear Grade				
≥65	1,607	50.8 (9.6)	<0.001	1.2×10^{-23}	I or II	3,464	48.3 (10.3)		
P _{trend}			<0.001		III	3,210	47.1 (10.6)	<0.001	0.870
BMI					Lymphatic or Vascular Invasion				
<25	2,412	47.7 (10.4)			No	5,097	48.0 (10.4)		
25-29	1,962	48.1 (10.3)	0.555	0.235	Yes	1,686	47.0 (10.5)	0.005	0.614
≥30	2,175	47.3 (10.6)	0.307	0.643	Tumor Size				
Race					0-1 cm	1,849	48.5 (10.1)		
White	7,002	47.8 (10.3)			1-2 cm	2,336	47.8 (10.4)	0.179	0.219
Hispanic	1,186	46.9 (10.8)	0.055	0.533	≥3	2,247	47.3 (10.7)	0.002	0.295
Education					Number of Positive Lymph Nodes				
Black	1,021	48.4 (10.7)	0.805	5.8×10^{-5}	0	3,737	48.2 (10.3)		
Asian/PI	490	48.1 (10.1)	1.000	0.275	1 or 2	1,587	47.5 (10.5)	0.152	0.305
Other	237	46.6 (10.7)	0.631	0.184	≥3	1,413	46.7 (10.5)	<0.001	0.186
Alcohol					Receptor Subtype				
HS or Less	2,516	47.3 (11.0)			HmR-positive	4,434	48.2 (10.3)		
Voc/AA	2,685	47.2 (10.6)	1.000	0.187	HER2-positive	995	46.8 (10.6)	0.001	0.050
College	4,548	48.4 (9.9)	<0.001	1.1×10^{-5}	Triple-negative	943	46.6 (10.9)	<0.001	0.079
Smoking					Menopause				
Never	4,897	48.2 (10.5)			Premenopause	4,017	48.4 (10.5)		
Former	757	45.3 (10.6)	<0.001	3.9×10^{-6}	Perimenopause	2,586	46.7 (10.3)	<0.001	0.546
Current	4,418	47.7 (10.2)	0.106	0.008	Postmenopause	191	47.3 (10.8)	0.565	0.509
Marital Status					Diagnosis Year				
Married	7,210	48.1 (10.1)			1999-2002	722	47.1 (10.7)		
Never Married	1,214	46.8 (10.8)	<0.001	0.056	2003-2007	2,593	47.6 (10.7)	0.522	0.430
Other	1,765	47.0 (11.2)	<0.001	1.8×10^{-5}	2008-2012	3,492	48.0 (10.2)	0.101	0.232
Past Medical History Score					Histology				
0	2,952	48.5 (9.9)			Ductal	5,421	47.5 (10.5)		
1	3,063	48.2 (10.3)	0.825	0.034	Lobular	584	48.6 (10.1)	0.127	0.339
2	2,180	47.4 (10.6)	0.001	5.3×10^{-11}	Mixed				
≥3	2,002	46.3 (11.0)	<0.001	1.1×10^{-21}	Ductal/Lobular	402	48.2 (10.2)	0.765	0.287
Previous Treatment					Other	400	48.4 (10.2)	0.576	0.481
None	5,876	47.9 (10.4)							
Yes	4,321	47.6 (10.4)	0.086	0.446					
Stage									
I	1,517	48.4 (10.3)							
II	2,071	47.8 (10.4)	0.382	0.183					
III	890	46.5 (11.3)	<0.001	0.885					

*Adjusted

3.3.6. Distribution of Determinants of QOL by Race

As shown in Table 8, there are racial disparities in PCS. To better understand the underlying explanation, we showed the distribution of determinants of PCS score by race (**Figure 8**). Fifty-six percent of Hispanics, 56% of Asian/PIs and 60% of Black patients discovered their breast cancer based on symptoms, which is a higher percentage compared to how White patients detected their cancer (50%) (**Figure 8A**). In addition, Black patients whose breast cancer was diagnosed based on symptoms reported on average an almost 5 point lower PCS score compared to Asian/PIs who were diagnosed based on symptoms (**Figure 8A**). Marital status was a strong predictor of a good QOL, with married patients reporting higher scores. When examining the distribution of marital status by race, Black patients had the lowest percentage of currently married patients at only 47%, compared to 80% of Asian/PI being married and 74% of White patients (**Figure 8B**) and Black and Hispanic patients reported lower PCS scores in the “Never Married” and “Other” group as well. An increasing trend in the percentage of patients with a high school diploma or less (a group that reported lower PCS scores) from Asian/PI (16%), White (23%), Black (29%), and Hispanic patients (44%) was seen (**Figure 8C**). When examining PCS scores by race in the patients who had completed high school or less, Blacks reported an average 6 points lower compared to Asian/PI (**Figure 8C**). When examining clinical characteristics, Hispanics had the largest proportion of patients who had three or more lymph nodes positive for cancer (26%) followed by Blacks (24%) (**Figure 8D**). Asian/PI had the lowest proportion of patients with three or more positive lymph nodes (18%) and those in that group reported higher PCS scores compared to other races in that group.

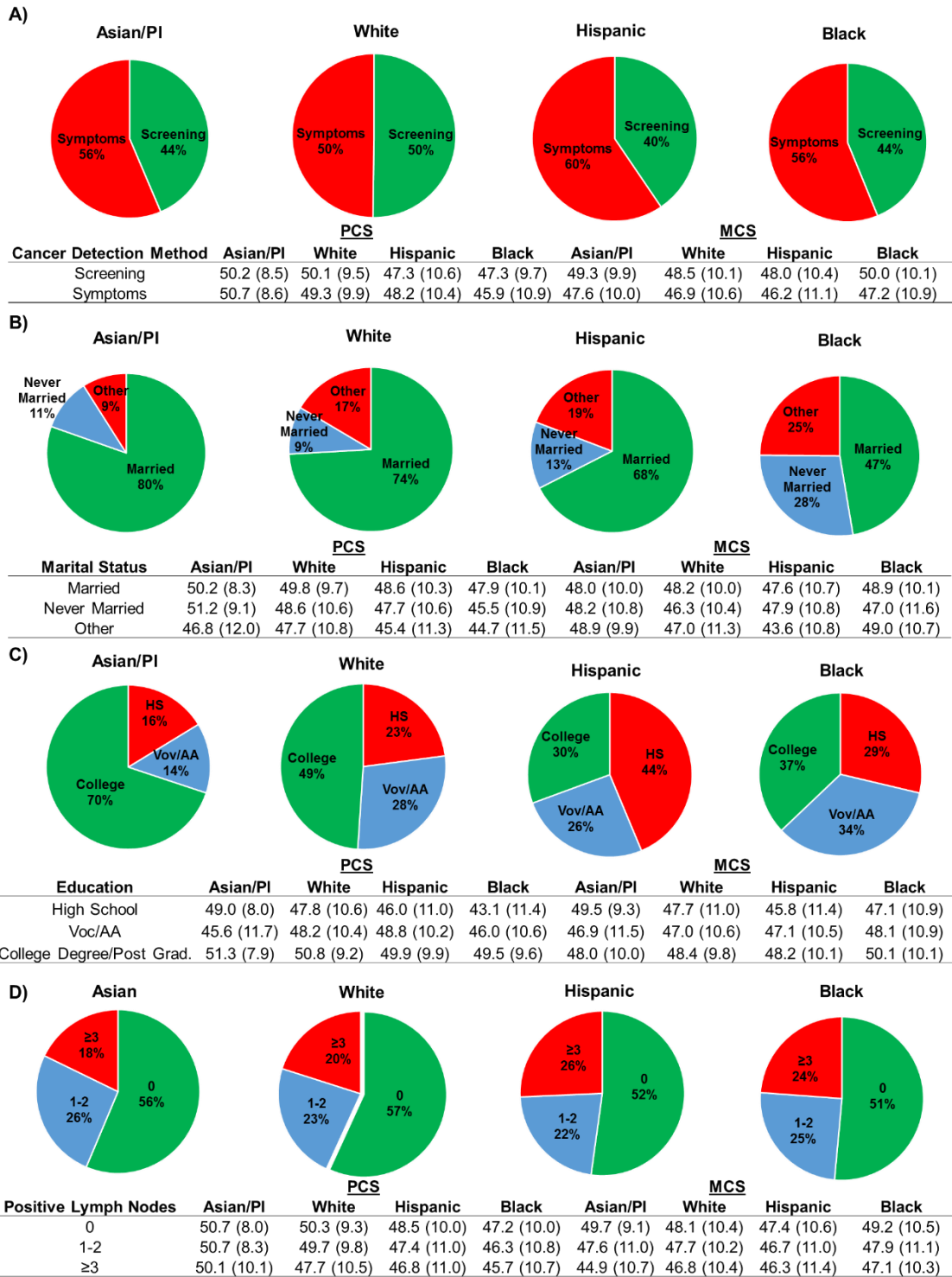


Figure 9. Distribution of determinants of QOL by race and corresponding QOL scores;

A) Cancer detection mode by race B) Marital status by race C) Education by race D)

Number of cancer positive lymph nodes by race

3.4. Discussion

The present study first examined the relationship between QOL and survival/recurrence in breast cancer patients. In the first section of the study, we found a dose response relationship between PCS score and survival. As PCS score decreased, the risk of death increased. For the second part of the study, predictors of QOL were analyzed and we aimed to further understand how the predictors of QOL were distributed by race. Significant predictors of a low PCS score included Hispanic and Black races, a higher BMI, never being married, finding breast cancer based on symptoms, having a nuclear III grade tumor, and triple-negative receptor status. Hispanic patients had the largest percentage of discovering their breast cancer due to symptoms, had the largest percent of patients with a high school degree or less, and were more likely to have three or more lymph nodes positive for breast cancer. Blacks had the lowest proportion of being married and Black patients who were “Never Married” or were in the “Other” group (separated, widowed, or divorced) and reported the lowest PCS scores compared to patients of other races in those groups. Asian/PI patients had the largest percentage of patients who were married and had the highest proportion of college educated patients and patients in these groups also reported the higher PCS scores. This is the first study to our knowledge that has comprehensively examined QOL predictors by race in newly diagnosed breast cancer patients. The results of this study can potentially be used to provide more data for patients that would identify from QOL interventions.

The current research on QOL in breast cancer patients does not include many studies on QOL and recurrence. One study found that better social well-being at diagnosis was associated with lower recurrence in breast cancer patients, but other domains of QOL and overall QOL were not associated with recurrence.(119) Other domains examined in that study included physical QOL, and while not significant due to a small number of events, the effect size was similar to our results(119). Specifically, a better physical QOL was associated with a reduced risk of recurrence(119). A benefit of examining recurrence in breast cancer patients is that the

outcome is specific. When examining survival in this study, we examined overall survival, which was not specific to breast cancer.

Previous studies have examined QOL around the time of breast cancer diagnosis and survival. For example, using data from the Shanghai Breast Cancer Survivor Study, one study found that breast cancer patients with a higher social well-being had a 38% decreased risk of death, but other QOL domains (physical, material, and psychological) were not associated with death(119). Social functioning is a subscale on the SF-12 and goes into calculating the MCS score. The MCS in our study were not significantly associated with survival, but a potential next step would be to look at subscales of the SF-12 individually. Other studies have examined domains of physical QOL. For example, in multivariate survival analyses, role function (the ability to perform normal daily activities) was significantly associated with survival(182). Another study found that physical QOL after disease relapse was associated with survival, specifically better physical well-being was associated with survival one month after relapse and six months after relapse. But that study did not find that baseline QOL was associated with survival(159). Our analysis showed that physical QOL was associated with overall survival. And specifically a dose response was seen, as QOL score decreased the risk of death increased. Our study used a comprehensive physical QOL score (the PCS) that encompasses many domains of physical QOL(58). The majority of previous studies regarding QOL and survival in breast cancer patients utilized domains of physical QOL rather than a comprehensive score.

Few studies have comprehensively examined predictors of QOL in breast cancer patients that are measured around the time of diagnosis. One study out of Munich examined predictors of QOL in breast patients within one year of their diagnosis with a sample size of 990 patients. But that study aimed to examine the simultaneous long-term effects of arm morbidity, communication, and comorbid conditions on long-term QOL and was not a comprehensive analysis(183). Another study examining predictors of QOL in breast and melanoma patients took a more psychological point of view and examined more of the psychological predictors of QOL (for example, predictors in the stress process and escape-avoidance coping were

associated with QOL)(184). One of our interesting results showed that patients who were never married reported lower physical QOL compared to their married counterparts. To our knowledge, this specific finding has not been reported before in the literature though there have been multiple studies on the benefits of marriage to the diagnosis and survival of breast cancer(185-187). One study that examined QOL predictors in a large sample of patients diagnosed with breast, urological, gastrointestinal, and gynecologic cancers found that non-married patients reported more depressive symptoms (a domain of QOL) compared to married patients or patients who lived with their partner(83). And another study reported that married breast cancer patients reported better social/family well-being and functional well-being QOL scores(188).

When we examined clinical factors, triple-negative breast cancer was a predictor of poor PCS score in unadjusted analyses. Triple-negative breast cancer is an aggressive subtype with poorer outcomes compared to other receptor subtypes. However, one study published on predictors of QOL in newly diagnosed breast cancer patients did not find any association between triple-negative breast cancer and QOL using the Functional Assessment of Cancer Therapy – Breast Cancer (FACT-B) questionnaire(188). Patients with triple-negative breast cancer are usually diagnosed with later stage disease and more aggressive disease, leading to more physical symptoms and limitations. When considering racial disparities, studies show that Black women are more likely to be diagnosed with triple-negative breast cancer(189). And we had found in our study that Black patients also reported worse PCS scores. The relationship between racial disparities and breast cancer is a complicated issue that needs further research.

We showed race is associated with poor survival, specifically that Black patients had worse overall survival and Asian/PI had the best survival, which is consistent with the literature(190). In addition, we found that QOL differed by race. We wanted to examine how determinants of QOL were distributed by race and subsequently how QOL scores differed by race and determinants to be able to more specifically identify patients at risk for poor QOL. When we examined how predictors of PCS score were distributed, we found intriguing results. First,

Black, Hispanic, and Asian/PI patients were more likely to have discovered their breast cancer based on symptoms instead of routine screening. Breast cancer screening rates have been shown to differ among races and this can partially be due to access to healthcare screenings(191, 192), which could potentially lead to women seeking treatment for breast cancer symptoms rather than seeing a physician on a regular basis for screening. To the best of our knowledge, there have not been any studies published on the distribution of women who discover their breast cancer via screening or symptoms and any association with physical QOL. In our study, Black and Hispanic women who discovered their cancer based on symptoms reported on average lower PCS scores compared to Whites and Asian/PI who discovered their cancer by symptoms. We hypothesize that this relationship could be due to the symptom burden that is experienced by breast cancer patients, which can be worse for Hispanic and Black women(193). Research also shows that a better QOL (including physical QOL) is predictive of a woman receiving her screening mammogram(194). Furthermore, another study found that older Black cancer patients were more at risk for depression if they had cancer symptoms (not specific to breast cancer) compared to asymptomatic patients(195). It is apparent that this finding is complicated and more research is needed. Potential next steps would be to look prospectively at what comes first, poor QOL across racial minorities which leads to poor screening for cancer, or the reverse.

Other predictors of PCS score that differed in distribution by race group included marital status and education. Marital status has been indicated as an important part of social support during cancer with impacts on QOL and cancer survival(186, 196-198). Our study showed that never married, separated, widowed, or divorced Black patients reported a lower PCS score and Blacks had the largest percentage of unmarried patients indicating a potential lack of social support. A study that examined predictors of QOL across races in breast cancer survivors found that social support is an important predictor of QOL across races except for Asian Americans(199). Education level was also a predictor of a poor PCS score in our study. Further, Hispanic and Black patients had the largest percentage of patients with a high school

degree or less and those patients reported lower QOL scores. Education level is considered a proxy for SES, and research has shown that breast cancer survivors that have a lower SES report lower QOL(200). These findings could be used to target interventions in racially diverse groups in the future with the intent of improving QOL and potentially survival.

Two major strengths of this study are the large sample size and the very detailed host and clinical characteristic data. Also, a large amount of follow-up time data was available. A potential limitation of this study is the lack of information on arm mobility due to surgery that may have removed lymph nodes and resulting lymphedema which could negatively impact QOL.

The findings of our study show that poor physical QOL and being Black or Hispanics are associated with poor survival and recurrence in breast cancer patients. To further examine the reasons underlying these associations, we found that a high BMI, being unmarried, detecting breast cancer based on symptoms, triple negative receptor subtype, and a high nuclear grade (among other factors) were predictors of poor physical QOL. Further, these determinants were disproportionately distributed more among Black or Hispanic patients. The results of this study highlight the importance of understanding racial disparities in cancer survival and the potential factors that may impact cancer survival. Potential interventions on cancer patients could be planned for future research that would target modifiable factors (such as obesity) with the hopes of improving QOL and cancer survival.

Chapter 4. Genetic Variants in the Dopaminergic System and Bladder Cancer Clinical Outcomes

4.1. Introduction

Bladder cancer is the fourth most common cancer and ranks eighth in cancer related death for men in the United States in 2017(1). Approximately 80% of patients are diagnosed with non-muscle invasive bladder cancer (NMIBC) and 50-80% will experience a recurrence, with approximately 14% of those patients going on to progress to muscle invasive bladder cancer (MIBC)(77). The standard initial treatment for NMIBC is transurethral resection (TUR). To reduce the risk of recurrence caused by tumor cell implantation following TUR, perioperative intravesical therapy is often given(201). Bacillus Calmette-Guerin (BCG) is the intravesical therapy most commonly given with the goal of delaying recurrence or progression of disease(72, 73). It is an immunotherapy that is thought to mount a local immune response(73). Though BCG is considered the gold standard for treatment of high-risk NMIBC, a subset of patients experience negative side effects (such as cystitis, increased urine frequency, hematuria, and fever)(202). Treatment for MIBC usually entails removal of the bladder and/or chemotherapy/radiation(74). Even after radical cystectomy in MIBC patients, half of patients will go on to develop metastasis and will die within 2-years(203). Management decisions for bladder cancer patients are based on clinical and pathological factors including number of tumors, the size of the tumors, prior recurrence, tumor grade, depth of invasion into the bladder wall, and the presence of carcinoma in situ (CIS)(204). Therefore, the defining feature of bladder cancer is the unfavorable clinical outcomes, specifically the high recurrence rate experienced by NMIBC patients. The identification of accurate predictive biomarkers are urgently needed to identifying patients who are at a higher risk of a poor clinical outcomes. Results in this area could guide future treatment and surveillance guidelines.

Currently, there lacks good molecular markers predictive of bladder cancer clinical outcomes. One area of biomarker interest is in genetics. Evidence supports a heritability to bladder cancer risk(66, 205). Currently, many bladder cancer susceptibility loci have been identified through large scale genome wide association study(206-210). But there are fewer studies that examined the association of genetic variants with bladder cancer clinical

outcomes(113, 209, 211). Several pathways have been examined for their association with bladder cancer outcomes such as the microRNA biogenesis pathway, the DNA repair pathway, detoxification pathways, and angiogenesis(212, 213). A recent study showed a validated single nucleotide polymorphism (SNP) in the micro-RNA biogenesis gene *DDX20* associated with a decreased risk of recurrence in NMIBC patients who have received TUR(213). This study used bootstrapping to internally validate SNP rs197412 and was also able to additionally validate the findings using a separate population and this variant was borderline significant(213). Other genes that have SNPs associated with bladder cancer clinical outcomes include *ERCC4*, *EPHX1*, and *CXCR2*. Variants in these genes have been associated with survival in MIBC patients, though these appear to not have gone through a validation phase of study(212). In addition, studies have also looked at treatment specific variants and the association with bladder cancer outcomes. For example, *SHH*: rs1233560 and *GLI2*: rs11685068 are associated with recurrence in NMIBC patients that receive TUR-only(209). Also, in bladder cancer patients that receive chemotherapy, multiple polymorphisms in *XRCC1* were protective for survival(214). A recent study by Lin et al. found that bladder cancer patients that are depressed at time of diagnosis show a worse survival(101), which leads to the question: Is there is a genetic component in patients with bladder cancer that also plays a role in depression?

The dopaminergic system plays a role in cognition, depression, addiction, pleasure, reward, and working memory(114). This system is also thought to play a role in immune function, as well as cancer growth(215). Further, smoking is one of the major risk factors for bladder cancer(61) and the dopamine system plays a major role in nicotine addiction(216-218). In addition, dopamine has a complex interaction in the brain with glutamate and GABA neurotransmission in the reward circuit(219). There are five subtypes of dopamine receptors encoded by the human genes *DRD1*, *DRD2*, *DRD3*, *DRD4*, and *DRD5* that control the majority of the physiological functions of dopamine(220). These receptors also impact cardiovascular, renal, and gastrointestinal functions(220). There are not many studies that have examined

genetic variants in the dopamine pathway and bladder cancer. One study that examined SNPs from major pathways involved in the carcinogenesis pathway did find a variant in *DRD4* to be associated with survival in bladder cancer patients, though this study did not do an in-depth analysis of variants in and related to dopamine(221). In this study, we aimed to perform a comprehensive analysis of genetic variants in the dopaminergic system and examine their associations with bladder cancer clinical outcomes utilizing the largest on-going bladder cancer epidemiology study in the United States – the Texas Bladder Cancer Study (TXBCS). We also assessed if there were associations between these genetic variants and clinical outcomes stratified by treatment regimens. We used a two-phase study design with a discovery and an external validation phase using an independent population. To our knowledge, this is the first study to comprehensively examine the associations between genetic variants in the dopamine pathway and bladder cancer clinical outcomes.

4.2. Methods

4.2.1. Study Subjects

Bladder cancer patients were recruited from The University of Texas MD Anderson Cancer Center and Baylor College of Medicine from 2007 to 2012. Patients were identified by trained study staff members from daily clinic schedules. Patients were diagnosed with histologically confirmed transitional cell carcinoma bladder cancer and were untreated. There were no restrictions in terms of age, sex, or stage of bladder cancer. All participants provided written informed consent prior to data and biospecimen collection and the Institutional Review Boards of MD Anderson Cancer Center and Baylor College of Medicine approved this study. Over 90% of recruited patients were Caucasian, therefore the analyses were limited to Caucasian patients to reduce the confounding effect of population structure.

An independent validation was completed using an on-going bladder cancer study in Europe: The Spanish Bladder Cancer (SBC)/Epidemiology of Cancer of the Urothelium (EPICURO). The SBC/EPICURO study recruited NMIBC and MIBC patients between 1998 and 2001 across 18 different hospitals (either general or university-affiliated) in five different geographical regions in Spain.

4.2.2. Data Collection

Recruited TXBCS patients completed an in-person interview with a trained staff member. The interview asked questions pertaining to age, sex, smoking history, occupational history, family medical history, personnel medical history, and nutrition. Current smokers were patients who had smoked at least one cigarette in the previous year. Former smokers were those who had not smoked one cigarette in the past year and never smokers were cases who had smoked less than 100 cigarettes in his or her lifetime. Clinical variables were abstracted from electronic medical records by trained staff. For the SBC/EPICURO study, trained interviewers conducted personal computer-assisted questionnaires at first hospital admission to collect sociodemographic and symptom data(222). Clinical data (diagnostic procedures, first

treatment, stage, and tumor characteristics) was abstracted by physicians using a structured questionnaire(222).

4.2.3. SNP Selection and Genotyping

For the discovery phase, patients provided a 40 milliliter (mL) peripheral blood sample at time of study recruitment to be used for genetic analyses. Genes related to the dopamine system were identified through KEGG and Reactome databases using the search words “dopamine” and “dopaminergic”. SNPs were within 10 kb from the start and end of gene transcription. For this study, 3,099 genetic variants in 178 genes were analyzed. The genotype data used for this study was from a previously completed genome-wide association study (GWAS) on bladder cancer. Detailed genotyping and quality control procedures were previously described(210). Briefly, the GWAS was completed using the Illumina’s Human-Hap610 BeadChip following the manufacturer protocol. Beadstudio software (Illumina) was used to export and analyze the genotyping data. The SBC/EPICURO validation SNPs were genotyped using the Infinium Illumina Human 1M probe BeadChip(209).

4.2.4. Statistical Analysis

The majority of the statistical analyses were performed using Stata 14 statistical software package (Stata Corporation, College Station, TX). Host characteristics (demographic and clinical variables) were analyzed using the Pearson’s χ^2 test or Fisher’s exact test if the variables were categorical and the Wilcoxon rank sum test or student’s t-test if the variables were continuous. Goodness-of-fit χ^2 analysis was used to test Hardy-Weinberg equilibrium. To analyze if there was an association between SNPs related to the dopamine pathway and bladder cancer clinical outcomes, multivariate proportional Cox regression was used. Hazard ratios (HR), 95% confidence intervals (CI), and p-values were calculated in the dominant, recessive, and additive model of genetic inheritance. Models were adjusted for age, gender, sex, smoking status, grade of disease, stage of disease, and treatment. Stratified analyses by treatment groups were conducted to examine whether the effect of genetic variants on clinical outcomes were modified by the treatment groups. The endpoints for this study were recurrence

and progression for NMIBC patients and survival for MIBC and metastatic patients. Recurrence was defined as having a recurring tumor following a cancer free cystoscopy. Progression was defined as progressing from a NMIB tumor to a MIB tumor. Time to event was calculated from date of diagnosis to date of event, or last contact, or death, whichever came first. Kaplan-Meier curves were generated for validated SNPs. Median recurrence time (MRT), median progression time (MPT), and median survival time (MST), and log-rank tests were calculated for patients stratified by each validated SNP. SNPs that had a p-value of less than 0.005 in the discovery phase of TXBCS were followed up in an independent population (SBC/EPICURO) for validation. In the validation, multivariate proportional Cox regression was used to analyze the association between SNPs and bladder cancer clinical outcomes.

4.3. Results

4.3.1. Host Characteristics

The patient characteristics are shown in **Table 10**. The median follow-up time for NMIBC patients with recurrence or progression was 78.2 months and 80.6 months, respectively. The median follow-up time for MIBC patients was 90.1 months. In total, there were 503 patients with NMIBC and 388 patients with MIBC (which includes patients with stage IV metastatic disease). When examining the NMIBC group, 270 patients experienced a recurrence and 94 patients experienced progression of disease. The majority of NMIBC patients were male and former smokers. The mean age in those who experienced a recurrence was 62.5. When examining recurrence, the majority of patients who had Ta disease and were high grade experienced a recurrence. There was a significant difference in those who had a recurrence and those who did not based on treatment. There were 153 patients in the maintenance BCG (mBCG) subgroup and 107 patients in the induction BCG (iBCG) subgroup. Those who had iBCG therapy only (and did not complete maintenance BCG therapy) had the highest number of recurrences. When examining progression, significant differences were seen for sex and age ($P=0.037$ and $P=0.023$, respectively). In the MIBC group, the majority of patients were male and former smokers as well. The mean age in patients who died was 67.6, which was significantly higher than those who were alive (61.9, $p<0.001$). There was a significant difference in survival status based on grade of disease, with the largest number of deceased patients having high grade (G3) disease.

Table 10. Host Characteristics in NMIBC and MIBC Patients

Table 1. Baseline Characteristics in NMIBC and MIBC Patients									
	NMIBC (N=503)					MIBC (N=388)			
	Recurrence N (%)			Progression N(%)			Survival N(%)		
Characteristic	Yes (N=270)	No (N=233)	P Value	Yes (N=94)	No (N=409)	P Value	Dead (N=230)	Alive (N=158)	P Value
Sex									
Male	224 (54.4)	188 (45.6)		84 (20.4)	328 (79.6)		172 (58.7)	121 (41.3)	
Female	46 (50.6)	45 (49.5)	0.508	10 (11.0)	81 (89.0)	0.037	58 (61.1)	37 (39.0)	0.685
Age (years)									
Mean (SD)	62.5 (11.4)	63.1 (12.0)	0.587	65.2 (9.1)	62.2 (12.1)	0.023	67.6 (10.8)	61.9 (10.0)	<0.001
Smoking Status									
Never	81 (54.7)	67 (45.3)		28 (18.9)	120 (81.1)		42 (52.5)	38 (47.5)	
Former	113 (54.3)	95 (45.7)		43 (20.7)	165 (79.3)		116 (63.4)	67 (36.6)	
Current	64 (54.2)	54 (45.8)	0.996	22 (18.6)	96 (81.4)	0.876	66 (57.4)	49 (42.6)	0.226
T Stage									
Ta	128 (57.4)	95 (42.6)		25 (11.2)	198 (88.8)		--	--	
Tis	22 (66.7)	11 (33.3)		10 (30.3)	23 (69.7)		--	--	
T1	119 (48.4)	127 (51.6)	0.044	58 (23.6)	188 (76.4)	0.001	--	--	
T2	--	--		--	--		139 (52.9)	124 (47.2)	
T3	--	--		--	--		40 (63.5)	23 (36.5)	
T4	--	--		--	--		48 (88.9)	6 (11.1)	<0.001
Grade									
G1	8 (36.4)	14 (63.6)		1 (4.6)	21 (95.5)				
G2	95 (54.6)	79 (45.4)		13 (7.5)	161 (92.5)		4 (30.8)	9 (69.2)	
G3	151 (52.4)	137 (47.6)	0.272	72 (25.0)	216 (75.0)	<0.001	218 (60.2)	144 (39.8)	0.034
Treatment NMIBC									
TUR	102 (62.2)	62 (37.8)		20 (12.2)	144 (87.8)		--	--	
iBCG	116 (75.8)	37 (24.2)		46 (30.1)	107 (69.9)		--	--	
mBCG	36 (33.6)	71 (66.4)		24 (22.4)	83 (77.6)		--	--	
Other	16 (20.3)	63 (79.8)	<0.001	4 (5.1)	75 (94.9)	<0.001	--	--	
Treatment MIBC									
TUR+Cystectomy	--	--		--	--		52 (44.4)	65 (55.6)	
TUR+Chemotherapy	--	--		--	--		59 (58.4)	42 (41.6)	
TUR+Cystectomy +Chemotherapy	--	--		--	--		44 (88.0)	6 (12)	
TUR Only	--	--		--	--		32 (74.4)	11 (25.6)	
Other	--	--		--	--		39 (55.7)	31 (44.3)	<0.001

4.3.2. Association between Dopamine Pathway SNPs and Recurrence and Progression of Bladder Cancer in NMIBC Patients

Recurrence

When analyzing the association between dopamine pathway SNPs and recurrence in NMIBC patients, 37 SNPs were significant with a p-value less than 0.005. However, none of the SNPs were validated in the independent SBC/EPICURO population.

Progression

A total of 24 SNPs were associated with progression in NMIBC patients. Three variants located in the Synaptotagmin 1 gene (*SYT1*) were validated (rs10861755, rs1245810, rs1245819) (**Table 11**). The three variants were in high linkage disequilibrium with an $R^2=1.00$ for rs10861755 and rs1245810, an $R^2=0.99$ for rs10861755 and rs1245819, and a $R^2=0.98$ for rs1245810 and rs1245819. The most significant variant associated with progression was rs1245819 (Discovery: HR=2.35, 95% CI: 1.34-4.11, P=0.003; Validation: HR=2.14, 95% CI: 1.18-3.89, P=0.013). The results of the meta-analysis was significant (HR_{Meta}:2.25, 95% CI: 1.50-3.38, P=0.0001) (P_{Heterogeneity}=0.82). The P_{Log-rank} test was significant (P_{Log-rank}=0.0008) and the MPT was not able to be calculated (**Figure 9**).

Table 11. Genetic Variants in the Dopamine Pathway and Progression in NMIBC Patients

Gene: SNP	Discovery					Validation				Meta-Analysis			
	Model	Minor Allele	Progression	No Progression	HR (95% CI)*	P Value	Progression	No Progression	HR (95% CI)**	P Value	HR (95% CI)	P Value	P _{Heterogeneity}
SYT1: rs10861755	Rec	G	94	409	2.35 (1.34-4.11)	0.003	83	752	2.02 (1.13-3.62)	0.017	2.19 (1.46-3.27)	0.0001	0.71
SYT1: rs1245810	Rec	A	94	409	2.35 (1.34-4.11)	0.003	83	752	1.88 (1.03-3.43)	0.038	2.12 (1.41-3.19)	0.0003	0.59
SYT1: rs1245819	Rec	G	94	409	2.35 (1.34-4.11)	0.003	83	752	2.14 (1.18-3.89)	0.013	2.25 (1.50-3.38)	0.0001	0.82

*Adjusted for age, sex, smoking, grade, treatment, and stage

**Adjusted for gender, age, and region

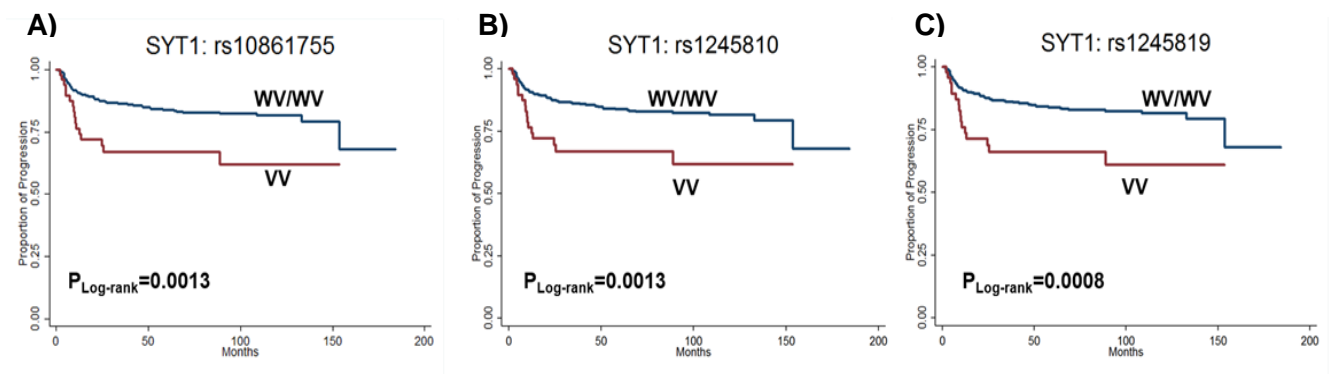


Figure 10. Kaplan-Meier curves of validated variants and progression in NMBIC patients;

A) SYT1: rs10861755 B) SYT1: rs1245810 C) SYT1: rs1245819

4.3.3. Genetic Predictors of Survival in MIBC Patients

Overall, 37 SNPs were associated with survival in MIBC patients at a p-value cut-off of 0.005. When comparing the results with the SBC/EPICURO population, no variants were validated.

4.3.4. Genetic Predictors of Recurrence and Progression in the TUR Only Group

Recurrence

A total of 47 SNPs in the discovery phase were significantly associated with recurrence in NMIBC patients that received TUR only. No variants were validated in the independent population.

Progression

Overall, 26 SNPs were significantly associated with progression in the discovery phase analysis in NMIBC patients only treated with TUR. Using the SBC/EPICURO population, one variant was validated (**Table 12**). In the discovery phase, patients with two copies of variant allele of *SLC1A1*: rs7848533 showed an almost six-fold (HR: 5.93, 95% CI: 2.05-17.15, $P=0.001$) increased risk of progression compared to patients who were wildtype or heterozygous. In the validation population, patients showed an almost three-fold ($HR_{SBC/EPICURO}$: 2.78, 95% CI: 1.36-5.68, $P=0.005$) increased risk of progression. This SNP was significant in the meta-analysis as well ($HR_{Meta}=3.52$, 95% CI: 1.95-6.37, $P=0.000032$) ($P_{Heterogeneity}=0.25$). The MPT was not able to be calculated as not enough people experienced progression. The KM curve was calculated (**Figure 10**) and a significant difference was seen between those who were in the wildtype/heterozygous groups versus the homozygous variant group ($P_{Log-rank}=0.0005$).

Table 12. The Association Between Dopamine SNPs and Progression in NMIBC Patients that Received TUR-Only

Gene: SNP	Model	Discovery				Validation				Meta-Analysis			
		Minor Allele	Progression	No Progression	HR (95% CI)*	P Value	Progression	No Progression	HR (95% CI)**	P Value	HR (95% CI)	P Value	P _{Heterogeneity}
<i>SLC1A1</i> : rs7848533	Rec	C	20	144	5.93 (2.05-17.15)	0.001	34	321	2.78 (1.36-5.68)	0.005	3.52 (1.95-6.37)	3.2x10 ⁻⁵	0.25

*Adjusted for age, sex, smoking, grade, treatment, and stage

**Adjusted for age, sex, and region

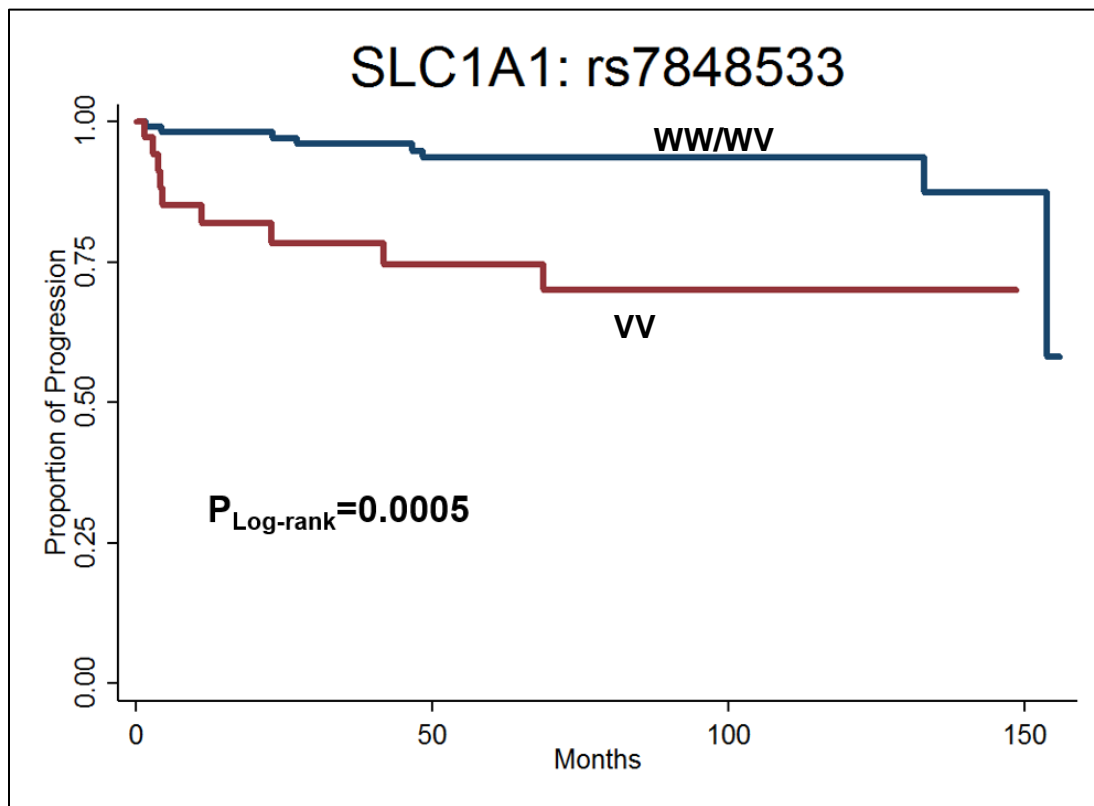


Figure 11. Kaplan-Meier curve of validated rs7848533 and progression in NMIBC patients that Received TUR

4.3.5. Genetic Predictors of Recurrence and Progression in the BCG Group

Recurrence

A total of 50 SNPs were associated with recurrence in NMIBC patients who had received BCG therapy in the discovery phase and one SNP was validated in the SBC/EPICURO population. The most significant result was *PLCB4*: rs6133707 which was associated with a 4.32-fold increased risk of recurrence (HR=4.32, 95% CI: 2.16-8.64, P=0.00004) in patients with two copies of the variant allele in the discovery phase. In the SBC/EPICURO validation phase, NMIBC patients with the homozygous variant allele showed an almost 4-fold increased risk of recurrence (HR_{SBC/EPICURO}=3.99, 95% CI: 1.86-8.57, P=0.0004) (**Table 13**). The results of the meta-analysis of the discovery and validation were significant (HR_{Meta}=4.17, 95% CI: 2.49-6.96, P=0.00000005) (P_{Heterogeneity}=0.88). When analyzing the KM curve, patients with wildtype or one copy of the variant allele had a MST of 15.8 months compared to 5.0 months for patients with two copies of the variant allele (P_{Log-rank}=0.002) (**Figure 11A**).

Progression

There were 38 SNPs associated with progression in NMIBC patients who received BCG therapy. Three variants were validated in the SBC/EPICURO population. After adjusting for potential confounders, patients with two variant alleles of *CAMK2A*: rs3776825 had an increased risk of progression (HR: 3.87, 95% CI: 1.90-7.89, P=0.0002) (**Table 13**). The KM curve (**Figure 11B**) showed a significant difference in median progression time for patients with two copies of the variant allele and patients who are wildtype or heterozygous (P_{Log-rank}=0.0007), with patients who have two copies of the variant allele having a median progression time of 88.9 months. The variant rs3776825 in *CAMK2A* was validated and was found to show an increased risk of progression in patients who have BCG therapy (HR_{SBC/EPICURO}=3.74, 95% CI: 1.58-8.87, P=0.003) (HR_{Meta}=3.82, 95% CI: 2.20-6.61, P=0.000002) (P_{Heterogeneity}=0.95) (**Table 13**). Two linked variants (R²=0.99) *SYT1*: rs10861755 and *SYT1*: rs1245810 were associated with an increased risk of progression in BCG treated patients (HR: 2.91, 95% CI: 1.62-5.22, P=0.0004). The KM curves showed that patients with

two copies of the variant have a MPT of 88.9 Months ($P_{\text{Log-rank}}=0.0007$) (**Figure 11C and 11D**). These variants validated using the SBC/EPICURO population and showed an almost 400% increase risk of progression ($HR_{\text{SBC/EPICURO}}=3.78$, 95% CI: 1.48-9.65), $P=0.006$) with the meta-analysis results also significant ($HR_{\text{Meta}}=3.13$, 95% CI: 1.91-5.14, $P=0.000007$) ($P_{\text{Heterogeneity}}=0.64$) (**Table 13**).

Table 13. Genetic Variants in the Dopamine Pathway and Recurrence and Progression in NMIBC Patients Who Received BCG Therapy

Gene: SNP	Model	Minor Allele	Discovery		Validation				Meta-Analysis				P _{Heterogeneity}
			Recurrence	No Recurrence	HR (95% CI)*	P Value	Recurrence	No Recurrence	HR (95% CI)**	P Value	HR (95% CI)	P Value	
<i>PLCB4</i> : rs6133707	Rec	G	152	108	4.32 (2.16-8.64)	4.0x10 ⁻⁵	69	200	3.99 (1.86-8.57)	0.00038	4.17 (2.49-6.96)	5.0x10 ⁻⁸	0.88

Gene: SNP	Model	Minor Allele	Discovery		Validation				Meta-Analysis				P _{Heterogeneity}
			Progression	No Progression	HR (95% CI)*	P Value	Progression	No Progression	HR (95% CI)**	P Value	HR (95% CI)	P Value	
<i>CAMK2A</i> : rs3776825	Rec	A	70	190	3.87 (1.90-7.89)	0.00019	30	239	3.74 (1.58-8.87)	0.003	3.82 (2.20-6.61)	2.0x10 ⁻⁶	0.95
<i>SYT1</i> : rs10861755	Rec	G	70	190	2.91 (1.62-5.22)	0.0004	30	239	3.78 (1.48-9.65)	0.0055	3.13 (1.91-5.14)	7.0x10 ⁻⁶	0.64
<i>SYT1</i> : rs1245810	Rec	A	70	190	2.91 (1.62-5.22)	0.0004	30	239	3.78 (1.48-9.65)	0.0055	3.13 (1.91-5.14)	7.0x10 ⁻⁶	0.64

*Adjusted for age, sex, smoking, grade, treatment, and stage

**Adjusted for age, sex, and region

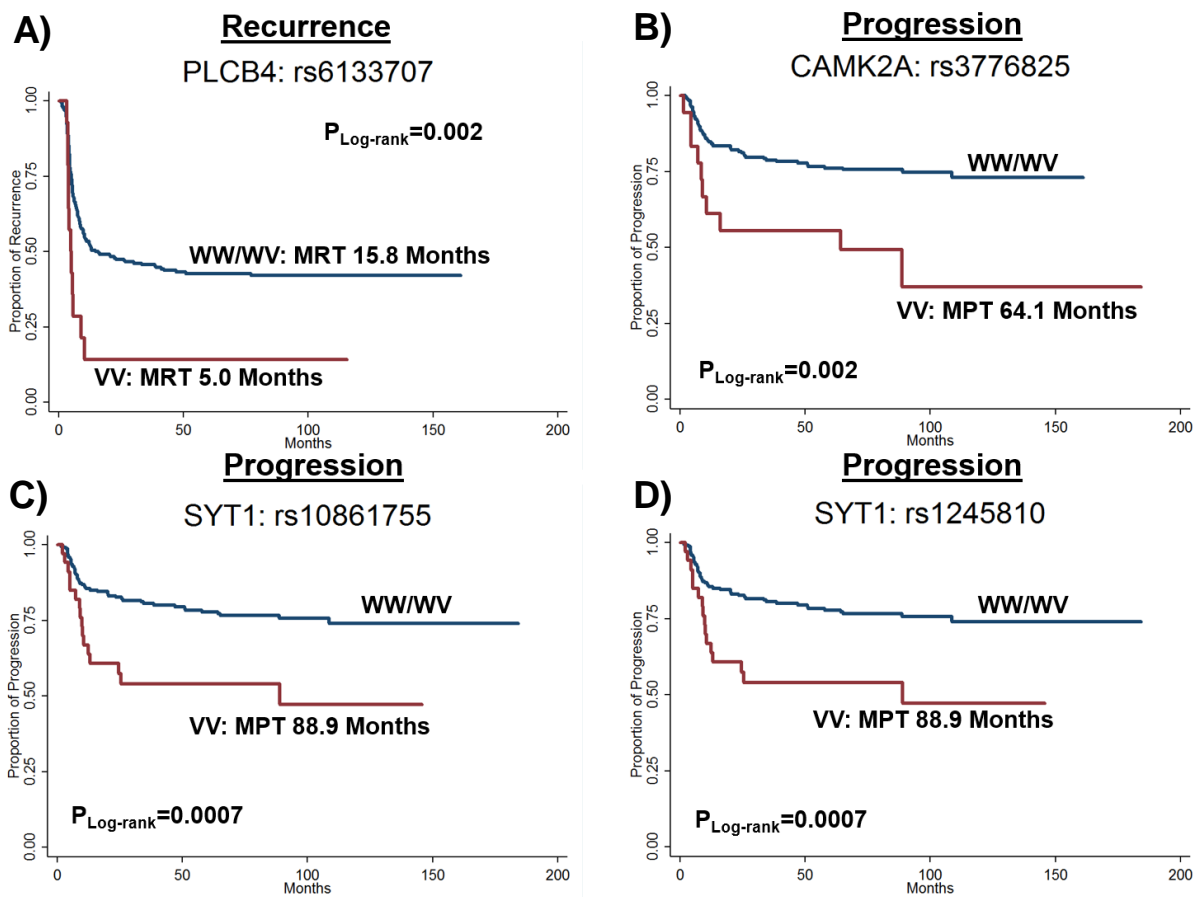


Figure 12. Kaplan-Meier curves of validated genetic variants Associated with recurrence and progression in NMIBC patients who received BCG therapy; A) *PLCB4*: rs6133707 B) *CAMK2A*: rs3776825 C) *SYT1*: rs10861755 D) *SYT1*: rs1245810

4.4. Discussion

The novel results of this study have the potential to aid in clinical decision making for patients with bladder cancer. Three highly linked SNPs in the dopamine pathway were associated with an increased risk of progression in NMIBC patients and were validated in the SBC/EPICURO population. Further, *SLC1A1*: rs7848533 was validated in the SBC/EPICURO population when examining the association with progression in patients who received TUR only, and was found to have an almost 6-fold increased risk of progression in the discovery phase and an almost 3-fold increased risk of progression in the validation phase. Finally, when restricting the analysis to patients who received BCG therapy, one variant was validated in the SBC/EPICURO population for risk of recurrence, and three variants validated for risk of progression. The validated SNPs based on the stratified analysis for treatment subgroups have the potential as the predictive biomarkers that could be used to identify high risk patients for more frequent monitoring or alternative treatment strategies. This is the first study to examine the association between genetic variants in the dopamine pathway and bladder cancer clinical outcomes.

The most significant SNPs associated with progression were all located in *SYT1*. NMIBC patients with two variants of rs10861755, rs1245810, or rs1245819 had a higher risk of progression. Furthermore, two of them (rs10861755 and rs1245810) were also associated with an increased risk of progression in patients who had received BCG therapy. These variants were not associated with progression in patients that received TUR-only and the effect size was not in the same direction. The gene *SYT1* encodes the protein Synaptotagmin 1, which plays a critical role in regulating neurotransmitter release in neurons(223-225). There is evidence that *SYT1* has a potential role in liposarcoma(226) but there has been no evidence of a role in bladder cancer. These variants are located on chromosome 12 and are intronic. More research is needed to understand the mechanism of these associations. Future steps include understanding the potential functional role of these variants.

When we examined progression in bladder cancer patients who received TUR only, rs7848533 in *SLC1A1* showed the highest risk of progression in patients with two copies of the variant allele. The results of our study are the first, to our knowledge, to examine the role of *SLC1A1* and bladder cancer. *SLC1A1* is a neuronal glutamate transporter that encodes EAAT3 (the excitatory amino acid transporter)(227) and glutamatergic input in specific regions of the brain cancer increases the activity of dopaminergic cells and increase dopamine release(228, 229). While mutations in this gene have been associated with mental health illness such as obsessive compulsive disorder(230), there are not many studies examining *SLC1A1* and its association with cancer. But the neurotransmitter that *SLC1A1* transports, glutamate, has been associated with cancer in the brain(231, 232) and other tissues (233, 234). The mechanism behind the association of rs7848533 and bladder cancer progression in TUR-only patients is not clear, but *SLC1A1* is expressed in bladder tissue providing evidence for a potential role in bladder cancer(235). Further studies are warranted.

Patients with NMIBC who had two copies of variant allele *PLCB4*: rs6133707 and who had received BCG therapy had an increased risk of recurrence. This finding was validated using SBC/EPICURO population. *PLCB4* controls processes such as neural signaling, synaptic plasticity, and cellular growth(236), and separate mutations in *PLCB4* have been linked to leptomeningeal melanocytic tumors and uveal melanoma(237, 238). The mechanisms underlying the association between *PLCB4* and bladder cancer is not clear, though *PLCB4* is expressed in bladder tissue(235). In addition, a variant (rs6056401) located in *PLCB4* has been shown to be protective against anxiety disorders with nominal significance(239). Because currently depressed bladder cancer patients show worse overall survival, we speculate that there is a potential relationship between mental health, genetics, and bladder cancer. More research is needed to further understand this relationship.

This is the first study to examine the association between SNPs in the dopamine pathway and bladder cancer clinical outcomes leveraging the largest on-going bladder cancer study in the United States with rich data. Another significant strength of this study is that a total of eight

variants were validated using an independent population (SBC/EPICURO). A potential limitation of this study is the small sample size for the treatment stratification analyses. For example, only 260 patients (70 of those 260 patients experienced progression) of the 503 NMIBC patients received BCG therapy. To offset this potential issue, we used a lower p-value cut-off for the discovery phase analysis. Further studies are needed to fully understand the mechanism of these variants on bladder cancer clinical outcomes. The findings from this novel study has the potential to stratify patients who are at higher risks for poor bladder cancer clinical outcomes and potentially be used to direct treatment options.

Chapter 5. Conclusions and Future Directions

This dissertation identified sociodemographic and clinical determinants of QOL in breast and lung cancer patients. Specifically, when examining sociodemographic factors, smoking, marital status, and education were predictors of physical and mental QOL in both lung and breast cancer patients. Further, a racial disparity existed when examining physical QOL in breast cancer patients. When examining how determinants of poor physical QOL were distributed among races, determinants of poor QOL were more prevalent among Hispanic and Black patients than whites. These results could be used to target individuals for interventions with the goal of improving physical and mental QOL. In addition, targeted interventions could hopefully bridge the gap in racial disparities of QOL in breast cancer patients. Finally, we identified eight SNPs in the dopamine pathway genes that were associated with bladder cancer outcomes (recurrence or progression). These results could potentially be used to identify patients at risk for poor outcomes of bladder cancer and could also potentially aid in treatment decisions by genetically testing patients.

Chapter 2 and **Chapter 3** of this dissertation focused on determinants of QOL in lung cancer patients and breast cancer patients. An interesting determinant from the research on lung cancer is that stage at diagnosis increased the risk of poor PCS or MCS more than any other determinant examined. It is very likely that those with later stage disease are experiencing worse symptom burden and higher mortality which could decrease QOL scores. Similar determinants were associated with PCS and MCS scores in breast and lung cancer patients which highlights that there is similarity in the determinants of QOL in cancer patients. While cancer sites have their own deficits in QOL and disease struggles (for example, lung cancer patients report very low QOL scores compared to other sites), this provides support that interventions could have wide applicability and target multiple cancer sites and do not necessarily have to be cancer site specific or could have components that are cancer site specific. For example, as education level increased average PCS and MCS scores increased as well in both populations. It is thought that education level can act as a proxy for SES, and research supports that baseline SES status is associated with poor QOL in lung cancer

patients(240) and breast cancer survivors(200). Another determinant associated with QOL in both populations was marital status. Specifically, divorced patients reported lower PCS and MCS scores in the lung cancer population and the “Other” group (which includes divorced patients) in marital status reported lower PCS and MCS scores in the breast cancer population. As stated previously, marital status itself is a prognostic factor for cancer survival(186). This relationship is likely due to a lack of social support and it makes sense that a lack of social support would negatively impact QOL scores as well.

An interesting finding in **Chapter 4** was the racial disparities that existed in QOL scores in breast cancer patients. It is well known that racial disparities exist in breast cancer clinical outcomes(60, 177, 178) and we found consistent results in our study population. We also showed that lower PCS scores were associated with lower overall survival. In this dissertation chapter we discovered that Hispanic and Black patients reported lower PCS scores compared to White patients and we aimed to further understand determinants that may impact this finding. Ideally, by understanding which factors affected QOL scores and were more concentrated in Hispanics and Blacks (groups that reported lower PCS scores) one could more specifically identify patients for interventions and possibly improve survival. Marital status was a determinant that was associated with QOL scores as discussed above in the previous paragraph. Black and Hispanic patients had higher proportions of “Never Married” and patients in the “Other” group (separated, divorced, and widowed) as well as slightly lower PCS scores in those groups compared to the other races. Other determinants associated with QOL that have disproportionate patterns in racial groups included number of positive lymph nodes. It is also possible that QOL differences reported by races are also due to differences in disease severity at diagnosis which should also be taken into consideration. Taking all of these factors together, you could potentially be able to more specifically target individuals to improve QOL in the clinic. Even potentially developing an easy to use checklist that includes these determinants for nurses and clinicians to better identify patients.

In **Chapter 2** of my dissertation, we focused on determinants of QOL and included a genetic component to our QOL study and examined genetic polymorphism in the p38 MAPK pathway and QOL scores as well as survival. It is difficult to state exactly what is occurring mechanistically between p38 MAPK and QOL. One hypothesized mechanism of action is that, as stated earlier, peripheral circulating pro-inflammatory cytokines activate the p38 MAPK pathway(131). It is possible that a higher levels of pro-inflammatory cytokines caused by existing depression(112, 241), the lung tumor itself(242), or from patient factors such as cigarette smoking(243) are excreting pro-inflammatory cytokines which in turn are activating the p38 MAPK pathway and is therefore producing more pro-inflammatory cytokines. Cytokines are large molecules but are able to cross the blood-brain barrier into the brain through leaky regions or through specialized transport molecules(112). It is possible that the pro-inflammatory cytokines are accessing the brain and inducing sickness behavior (which has many overlapping symptoms of depression) by altering neurotransmitters such as dopamine, norepinephrine, and serotonin(112). It is not entirely clear how the variant we validated (*MEF2B*: rs2040562, associated with an increase risk in poor mental health) mechanistically is involved, although as stated before increased expression of this gene is associated with depression in cancer patients(156) and is also associated with obsessive-compulsive disorder (OCD)(244) indicating a role in mental health. Depression is a domain of the MCS score from the QOL measure we used in this study and overall is an important domain of QOL.

Another possibility regarding the mechanism between the p38 MAPK pathway and QOL relates to activation of this pathway in the brain, leading to downstream negative effects. Research shows that the p38 MAPK pathway is highly activated in neurons in the brain with important roles in learning, memory, and synaptic plasticity(245, 246). For example, p38 MAPK can alter neurotransmitter function through the serotonin transporter SERT (encoded by *SLC6A4*)(153). Activation of SERT leads to the reuptake of serotonin and has been associated with many mood disorders such as depression, obsessive compulsive disorder, and suicide. Further studies have also found that elevated pro-inflammatory cytokines such as IL-1 and

TNF-alpha (activators of the p38 MAPK pathway) are associated with decreased cerebrospinal fluid (CSF) concentrations of serotonin metabolites, indicating activation of SERT(247). What is also very interesting, is in **Chapter 4** of my dissertation I examined variants in the dopamine pathway and bladder cancer clinical outcomes. The dopamine pathway was of interest due to its associations with depression. Research evidence supports that activation of the p38 MAPK pathway can produce cytokines in the brain that then affect the reuptake of neurotransmitters such as dopamine(248). Specifically, activation of MAPK pathways has been shown to affect the dopamine transporter (increase reuptake of dopamine) in cell lines, and this effect is blocked when using MEK inhibitors(249). This provides evidence of the complex nature of the biological role of QOL. This also provides rational for completing a more systemic comprehensive genetic analysis including all relevant pathways of QOL across multiple cancer sites.

In **Chapter 4** of my dissertation, we validated eight genetic variants from the dopamine pathway with bladder cancer clinical outcomes in NMIBC. Three variants in *SYT1* were associated with overall progression, one variant in *SLC1A1* was associated with progression in patients that received TUR-only, one variant in *PLCB4* was associated with recurrence in patients that received BCG therapy, and one variant in *CAMK2A* and two variants in *SYT1* were associated with progression in patients that received BCG therapy. It is not clear if mechanistically dopamine variants are affecting bladder cancer outcomes through peripheral action or from action in the brain that results in a change in clinical outcomes through mood. Peripherally, dopamine that is secreted has been shown to have anti-tumor effects through blocking angiogenesis and therefore stopping tumor growth(215). While studies have not been completed examining bladder cancer specifically, dopamine receptors are present in the bladder(116) and genes from this dissertation with validated variants are expressed in bladder tissue (specifically *SLC1A1*, *CAMK2A*, and *PLCB4*)(235). And the results of this chapter provide support for further functional studies to understand how and if dopamine is acting in the bladder. Conversely, it is possible that variants in the dopamine pathway are acting in the brain

and impacting the processing of dopamine. Which coupled with or without environmental factors and stressors could lead to depressive symptoms and poor clinical outcomes. Stress and depression have both been associated with clinical outcomes such as progression of cancer(104).

When taking these genetic results into a larger context, it is possible that validated variants such as the ones discovered in **Chapter 2** and **Chapter 4** could be used in the future for genetic testing of patients and become a component of personalized medicine. Research already supports a genetic component to depression(250) as well as variants that have been identified that are associated with a decrease response to antidepressant therapy(112), which further supports a genetic component to QOL (as depression is a domain of QOL) and stresses the importance of direct clinical use. It is important to mention that the relationship between genetic variants and phenotypes such as QOL or depression are associations. QOL has a complex etiology, as has been shown in this dissertation, but genetics plays an important role and it is very possible that QOL is polygenic. Which means that more comprehensive analyses are needed that also include variants known to be associated with domains of QOL, such as depression. In the future, if personalized medicine reaches the point where patients are tested for common genetic variants, the genetic results from this dissertation (with further validation) could potentially be included. For example, lung cancer patients (or with further studies, patients with other cancers as well) would be tested for a panel of polymorphisms that have been validated for associations with QOL. Then based on those results and combined with host determinant information, specialized interventions would be used. In terms of mental QOL interventions, antidepressant therapy could be prescribed in addition to talk therapy and social support groups. The results from **Chapter 4**, with further validation, could identify patients at risk for progression of bladder cancer. In the clinic, clinicians could use this genetic information to better identify patients in need of more aggressive therapy or treatment options. This could include frequent cystoscopies to look for progression of bladder cancer or more aggressive treatment options such as cystectomies.

A striking result from my dissertation in **Chapter 2** is the association between low PCS or low MCS in lung cancer patients and an increased risk of death, even after controlling for stage at diagnosis. Our findings were not just seen in lung cancer patients, we also saw this relationship in **Chapter 3** between PCS score and overall survival in breast cancer patients. Given how many domains go into determining a QOL score, there are many hypothesized reasons for this relationship. For example, patients that report poor QOL scores may be less likely to follow medical treatment fully to gain maximum benefit and therefore could shorten survival. Research has shown that patients that report low QOL are less likely to adhere to medical advice compared to patients who report better QOL(26, 251). The worse a patient is feeling in terms of QOL (for example the more depressed they are, the more they are experiencing physical limitations) they could be less likely to attend treatment appointments for fear of feeling worse or are less likely to be willing to participate in things that may improve their QOL. Further, domains of QOL such as depression also have been associated with poor cancer survival(252). Depression is very prevalent in the general population(252). If a person is already dealing with depression or more prone to depressive episodes, it is possible they would report lower QOL scores in the mental domain. Finally, another possible explanation for the relationship between QOL and cancer survival is that QOL may be a proxy for SES(200). For example, studies have shown that SES at baseline is associated with QOL in lung cancer patients(240). Further, evidence also supports that a higher SES is associated with better survival in cancer patients(253). Therefore it is a possibility that cancer patients with a higher SES would report higher QOL and show better survival. It is very clear that many factors play into QOL and the relationship with survival in cancer patients. It is not likely one factor that is underlying this relationship.

The ultimate goal of this dissertation is to understand determinants of QOL with the hopes of in the future improving QOL and therefore improving survival. When examining ways of improving QOL, the idea is to be able to identify patients at high risk of poor QOL or who are reporting a poor QOL and identify the factors that may be impacting their QOL. Then be able to

intervene early during a cancer diagnosis with the goal of improving QOL. Determinants of QOL can be thought of as modifiable and non-modifiable. Examples of modifiable factors would be determinants such as smoking status or alcohol usage as well as factors that are considered to be modifiable but are not likely to change dramatically (such as marital status or education level). Examples of non-modifiable factors are genetics, age, and past medical history. When thinking in terms of clinical interventions, the obvious target would be to intervene in modifiable factors with the hopes of improving QOL. An example of this would be smoking cessation programs. But there are also non-modifiable factors (or factors that are not easily modified) that should be taken into consideration. For example, it is not easy to modify marital status. If a patient is single or widowed it is not likely or easy to change that situation. And those patients could be lacking social support which could negatively impact QOL. What could potentially be done is to target those patients for support groups or peer mentoring groups with the goal of improving social support. Because of how multifaceted QOL is and the many determinants that impact QOL scores, interventions should be comprehensive and multifaceted as well. Even when intervening in patients with a devastating diagnosis, such as stage IV lung cancer that is not curative, the goal would still be to prolong survival by improving QOL. Examples of promising interventions include web based that are completed by the patient at home(254) and interventions that target QOL and domains of QOL (such as fatigue, body-image, stress, anxiety, and depression)(255). Our results provide even more support for the importance of these interventions and gives detailed determinant information that could be used to identify patients that could be approached for interventions.

In a clinical setting, QOL scores could be implemented in a patient's medical chart with easy access for the clinician (scores could be provided with general patient summary information). Research supports that QOL scores implemented in a clinical setting have additional benefits of improving patient-physician communication, especially around sensitive subjects as well as non-medical concerns(256, 257). As stated in previous studies, in order for this to be efficient it is imperative that easy to use and interpret measures are used(162). The

SF-12v1 that was used for this dissertation was only 12 questions and was easy for patients to complete. In addition, it was grouped together with additional patient entry information questionnaires, which increases the ease of completing the questionnaire as it becomes part of routine paperwork. Because of the strong association between QOL and survival, it is also imperative to perform targeted interventions on vulnerable patients that are identified in a clinical setting because of the potential to be cost effective. Patients that have improved QOL that go on to have improved outcomes could require less frequent and less expensive medical treatment. Further, QOL assessments should be completed regularly at clinic visits to follow trends of QOL and identify patients who may be having issues that weren't present at baseline measurement(123).

Future directions include an even more in-depth analysis of determinants of QOL. For example, obtaining information on physical activity level of patients and sitting time could aid in specific areas that could be targeted for intervention studies. For the genetic analysis in bladder cancer patients, conducting further functional studies on the validated SNPs will be needed to find the molecular mechanisms underlying the link between dopamine pathway and bladder cancer outcomes. Systemic study of genetic determinants of QOL and their impacts on patient outcomes will be a major effort in the future.

Taken together, our study provides a comprehensive overview of QOL in lung and breast cancer patients and supports a role of QOL-related genetic variations on bladder cancer patient outcomes. The results support that QOL is a crucial component of patient care.

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Appendix: Supplementary Tables

Supplemental Table 1. Association of Host Characteristics and PCS Scores

Host Characteristic	PCS<50	PCS≥50	OR (95% CI)	P Value
Age (Continuous)	4376	1329	1.00 (1.00-1.01)	0.246
Sex				
Male	2295	735	1.00 (Ref)	
Female	2081	594	1.09 (0.95-1.26)	0.215
Education				
< High School	596	102	1.00 (Ref)	
High School/Vocational/AA	2603	687	0.76 (0.60-0.97)	0.026
College Degree	1177	540	0.50 (0.39-0.64)	8.7x10 ⁻⁸
Alcohol Use				
Never	1914	423	1.00 (Ref)	
Former	909	159	1.11 (0.90-1.37)	0.343
Current	1553	747	0.50 (0.43-0.58)	1.0x10 ⁻¹⁶
Smoking Status				
Never	690	298	1.00 (Ref)	
Former	2813	839	1.34 (1.11-1.61)	0.002
Current	873	192	1.81 (1.43-2.31)	1.3x10 ⁻⁶
Past Medical History				
Yes	3733	1080	1.00 (Ref)	
No	643	249	0.75 (0.63-0.90)	0.002
Marital Status				
Married	3164	1026	1.00 (Ref)	
Widowed	453	109	1.19 (0.93-1.53)	0.166
Separated	24	6	1.10 (0.42-2.86)	0.850
Divorced	455	95	1.36 (1.06-1.74)	0.014
Never Married	280	93	0.96 (0.74-1.26)	0.787
Race				
White	3631	1127	1.00 (Ref)	
Hispanic	178	55	0.95 (0.68-1.33)	0.763
Black	346	68	1.18 (0.88-1.57)	0.268
Asian/Pacific Islander	145	56	0.87 (0.61-1.22)	0.409
Other	76	23	1.00 (0.60-1.65)	0.995
Past Treatment				
Yes	1400	211	1.00 (Ref)	
No	2976	1118	0.40 (0.32-0.50)	4.4x10 ⁻¹⁶
Histology				
Non-Small Cell				
Adenocarcinoma	2093	731	1.00 (Ref)	
Squamous Cell	720	190	1.41 (1.16-1.72)	0.001
Large Cell	155	36	1.36 (0.92-2.02)	0.122

Non-small cell carcinoma – non-specified	727	186	1.14 (0.94-1.39)	0.178
Small Cell	519	105	1.34 (1.05-1.71)	0.018
Other	162	81	0.93 (0.68-1.27)	0.641
Stage				
I	338	226	1.00 (Ref)	
II	114	87	0.79 (0.56-1.11)	0.167
III	612	270	1.45 (1.15-1.84)	0.002
IV	1276	322	2.79 (2.23-3.50)	<1.0x10 ⁻⁶³
Unknown	2036	424	2.02 (1.58-2.58)	1.7x10 ⁻⁸

Supplemental Table 2. Association of Host Characteristics and MCS Scores

Host Characteristic	MCS<50	MCS≥50	OR (95% CI)	P Value
Age (Continuous)	3255	2450	0.98 (0.98-0.99)	5.0x10 ⁻⁸
Sex				
Male	1631	1399	1.00 (Ref)	
Female	1624	1051	1.41 (1.26-1.59)	6.8x10 ⁻⁹
Education				
< High School	483	215	1.00 (Ref)	
High School/Vocational/AA	1902	1388	0.58 (0.48-0.70)	9.4x10 ⁻⁹
College Degree	870	847	0.50 (0.41-0.61)	1.8x10 ⁻¹¹
Alcohol Use				
Never	1360	977	1.00 (Ref)	
Former	668	400	1.20 (1.02-1.40)	0.025
Current	1227	1073	0.90 (0.80-1.02)	0.107
Smoking Status				
Never	483	505	1.00 (Ref)	
Former	2089	1563	1.40 (1.19-1.65)	3.8x10 ⁻⁵
Current	683	382	1.69 (1.38-2.06)	2.9x10 ⁻⁷
Past Medical History				
Yes	2777	2036	1.00 (Ref)	
No	478	414	0.77 (0.66-0.90)	0.001
Marital Status				
Married	2348	1842	1.00 (Ref)	
Widowed	311	251	0.91 (0.75-1.11)	0.362
Separated	22	8	1.84 (0.80-4.26)	0.153
Divorced	359	191	1.24 (1.02-1.50)	0.029
Never Married	215	158	0.94 (0.75-1.18)	0.606
Race				
White	2718	2040	1.00 (Ref)	
Hispanic	133	100	0.95 (0.72-1.26)	0.726
Black	258	156	1.00 (0.81-1.25)	0.975
Asian/Pacific Islander	92	109	0.72 (0.54-0.98)	0.035
Other	54	45	0.88 (0.58-1.33)	0.552
Past Treatment				
Yes	971	640	1.00 (Ref)	
No	2284	1810	1.00 (0.84-1.19)	0.985
Histology				
Non-Small Cell				
Adenocarcinoma	1547	1277	1.00 (Ref)	
Squamous Cell	519	391	1.12 (0.95-1.31)	0.173
Large Cell	111	80	1.00 (0.74-1.36)	0.992

Non-small cell carcinoma – non-specified	545	368	1.10 (0.94-1.29)	0.244
Small Cell	408	216	1.32 (1.09-1.59)	0.004
Other	125	118	0.99 (0.75-1.31)	0.954
Stage				
I	252	312	1.00 (Ref)	
II	85	116	0.86 (0.61-1.20)	0.361
III	495	387	1.55 (1.24-1.94)	9.8x10 ⁻⁵
IV	943	655	1.76 (1.43-2.16)	6.2x10 ⁻⁸
Unknown	1480	980	1.81 (1.45-2.27)	2.0x10 ⁻⁷

Supplemental Table 3. Association Between p38 MAPK Variants and PCS/MCS Scores

Discovery Phase					
PCS					
Gene: SNP	Model	PCS <50 WW/WV/VV	PCS ≥50 WW/WV/VV	*OR (95% CI)	P Value
<i>TNFRSF1B</i> : rs496888	Dom.	120/88/14	36/51/12	0.40 (0.21-0.75)	0.004
<i>MAPK11</i> : rs909692	Dom.	83/110/28	20/62/17	0.35 (0.17-0.73)	0.005
<i>MAP2K6</i> : rs2716191	Dom.	78/91/53	22/51/26	0.37 (0.19-0.75)	0.006
<i>MAP2K6</i> : rs2715812	Dom.	113/93/16	36/53/10	0.42 (0.22-0.78)	0.006
<i>MAP2K6</i> : rs2074028	Dom.	94/98/30	29/50/20	0.41 (0.21-0.79)	0.008
<i>MAP3K5</i> : rs11755484	Dom.	190/32/0	95/3/1	4.85 (1.50-16.02)	0.010
<i>MEF2B</i> : rs12459686	Rec.	72/118/32	34/43/22	0.36 (0.17-0.78)	0.010
<i>MAP2K6</i> : rs989681	Dom.	60/100/62	18/50/31	0.36 (0.16-0.79)	0.011
<i>MAP2K6</i> : rs2716227	Dom.	70/98/54	19/52/28	0.40 (0.19-0.83)	0.014
<i>MEF2B</i> : rs3761081	Add.	145/70/7	56/35/8	0.53 (0.32-0.88)	0.014
<i>MEF2A</i> : rs325381	Dom.	178/42/2	67/28/4	0.42 (0.21-0.85)	0.015
<i>MAP2K4</i> : rs1870584	Dom.	66/117/39	40/43/16	2.15 (1.12-4.12)	0.022
<i>MAP3K5</i> : rs9494569	Add.	67/118/37	37/55/7	1.75 (1.08-2.84)	0.023
<i>MAP2K4</i> : rs12942507	Dom.	93/102/27	52/38/9	2.05 (1.10-3.81)	0.023
<i>MAPK14</i> : rs13196204	Add.	159/56/7	64/28/7	0.54 (0.31-0.92)	0.024
<i>TNF</i> : rs1800629	Add.	174/43/5	72/22/5	0.51 (0.28-0.92)	0.024
<i>MAP2K6</i> : rs2521365	Dom.	114/81/27	41/47/11	0.51 (0.28-0.93)	0.028
<i>MEF2D</i> : rs1171556	Dom.	182/39/1	70/25/4	0.45 (0.22-0.92)	0.029
<i>MEF2A</i> : rs12593522	Add.	167/51/4	66/27/6	0.54 (0.31-0.94)	0.030
<i>MAP2K3</i> : rs1466314	Dom.	128/74/20	42/48/9	0.52 (0.29-0.95)	0.032
<i>MAP2K4</i> : rs8082185	Rec.	116/96/10	52/39/8	0.23 (0.06-0.89)	0.033
<i>MEF2D</i> : rs1750304	Dom.	184/38/0	70/26/3	0.47 (0.24-0.95)	0.035
<i>TNFRSF1B</i> : rs17037696	Rec.	136/70/16	65/33/1	9.84 (1.14-85.33)	0.038
<i>MAPK11</i> : rs6010226	Add.	75/110/36	20/60/19	0.62 (0.40-0.98)	0.040
<i>TNF</i> : rs2009658	Dom.	148/65/9	73/25/1	1.99 (1.02-3.87)	0.043
<i>TNFRSF1B</i> : rs1061624	Rec.	77/81/64	34/48/16	2.17 (1.02-4.61)	0.043
<i>MAPK11</i> : rs2076139	Add.	124/80/18	66/31/2	1.71 (1.02-2.88)	0.044
<i>MAP2K4</i> : rs9303045	Add.	63/111/48	26/46/27	0.65 (0.43-0.99)	0.046
<i>MAP2K6</i> : rs9302900	Dom.	123/83/16	65/27/7	1.84(1.00-3.39)	0.049
MCS					
Gene: SNP	Model	MCS <50 WW/WV/VV	MCS ≥50 WW/WV/VV	*OR (95% CI)	P Value
<i>MAP2K3</i> : rs1466314	Dom.	79/71/19	91/51/10	2.25 (1.31-3.87)	0.003
<i>TRAF2</i> : rs3739942	Rec.	90/58/21	90/58/4	5.43 (1.55-18.95)	0.008
<i>TNFRSF1B</i> : rs1061628	Rec.	58/91/20	54/66/32	0.41 (0.20-0.81)	0.011
<i>TNFRSF1A</i> : rs4149578	Dom.	143/25/1	117/34/1	0.43 (0.22-0.83)	0.011
<i>MAP2K6A</i> : rs2715815	Add.	68\82\19	47\80\25	0.62 (0.41-0.93)	0.021
<i>MAP2K6</i> : rs9302900	Rec.	95\59\15	93\51\8	3.97 (1.21-13.01)	0.023
<i>MAP2K3</i> : rs9899521	Add.	111\51\7	80\59\12	0.60 (0.39-0.93)	0.024
<i>MAP2K6</i> : rs2028049	Rec.	76\63\30	69\70\13	2.61 (1.13-6.00)	0.024

<i>MEF2A</i> : rs10902549	Dom.	55\78\36	31\82\39	0.51 (0.28-0.94)	0.031
<i>MAP2K6</i> : rs6501328	Rec.	92/62/15	84/60/8	3.31 (1.11-9.90)	0.032
<i>MAP2K4</i> : rs12942507	Dom.	83/63/23	62/77/13	0.56 (0.32-0.96)	0.034
<i>TRAF2</i> : rs10781522	Rec.	60/71/38	55/82/15	2.18 (1.05-4.54)	0.037
<i>FAS</i> : rs6586163	Dom.	40/87/42	25/92/35	0.49 (0.25-0.96)	0.037
<i>MAP2K6</i> : rs11651488	Rec.	98/57/14	94/51/7	3.15 (1.07-9.30)	0.037
<i>MEF2A</i> : rs325383	Rec.	78/68/23	86/59/7	2.83 (1.06-7.55)	0.038
<i>FASLG</i> : rs10458360	Rec.	49/85/35	47/85/20	2.13 (1.04-4.38)	0.039
<i>MEF2B</i> : rs2040562	Rec.	86/60/23	75/70/7	3.06 (1.05-8.92)	0.041
<i>TNFRSF1B</i> : rs5745984	Dom.	156/13/0	150/2/0	5.34 (1.05-27.21)	0.044
<i>TNF</i> : rs2009658	Rec.	113/47/9	108/43/1	9.58 (1.02-89.75)	0.048
<i>MAP2K4</i> : rs8064513	Rec.	83/69/17	71/71/10	2.86 (1.01-8.08)	0.048

Abbreviations: OR-Odds Ratio, Dom.-Dominant, Rec.-Recessive, Add.-Additive

*Adjusted for age, sex, race, education, marital status, alcohol use, smoking status, past medical history, prior cancer treatment, histology, and cancer stage

Supplemental Table 4. Association between Genetic Variants in the p38 MAPK Pathway and 5-Year Overall Survival

	Model	Dead WW/WV/VV	Alive WW/WV/VV	*HR (95% CI)	P Value	Model MST (Months)	P _{log-rank}
MAP3K5: rs3765259	Dom.	66/111/59	17/46/22	0.56 (0.40-0.79)	0.0008	WW/WW+WV 17.31/23.75	0.053
MAP2K6: rs817545	Rec.	55/116/65	27/41/17	1.70 (1.23-2.35)	0.001	WW+WV/VV 23.10/17.45	0.152
MAP2K6: rs4968791	Rec.	65/107/59	29/43/13	1.68 (1.20-2.35)	0.003	WW+WV/VV 23.75/17.45	0.066
MAPK11: rs909692	Rec.	75/125/35	28/47/10	1.82 (1.21-2.73)	0.004	WW+WV/VV 22.93/18.10	0.180
MAP2K6: rs2716195	Dom.	173/57/6	55/26/4	0.62 (0.44-0.88)	0.006	WW/WV+VV 21.32/26.74	0.108
TNFRSF1B: rs7552664	Rec.	144/80/12	47/28/10	0.39 (0.19-0.80)	0.011	WW/WV+VV 21.52/49.09	0.030
MAP2K6: rs6501328	Dom.	131/86/19	45/36/4	0.69 (0.51-0.93)	0.016	WW/WV+VV 23.03/21.59	0.672
MEF2B: rs12609573	Add.	68/116/52	33/38/14	1.28 (1.03-1.58)	0.023	WW/WW+WV/WW+WV+VV 30.55/21.49/18.37	0.033
MAPK11: rs6010226	Add.	74/117/44	21/53/11	1.29 (1.03-1.61)	0.026	WW/WW+WV/WW+WV+VV 22.44/24.51/16.99	0.049
MEF2B: rs12459686	Add.	87/115/34	19/46/20	0.79 (0.63-0.98)	0.032	WW/WW+WV/WW+WV+VV 18.37/23.06/33.94	0.023
MAP2K6: rs2715825	Rec.	105/110/21	30/40/15	0.53 (0.30-0.95)	0.033	WW+WV/VV 21.88/29.63	0.065
MEF2D: rs16837415	Dom.	205/30/1	79/6/0	1.69 (1.04-2.73)	0.034	WW/WW+WV 21.88/22.57	0.278
MAPK14: rs851006	Dom.	136/82/18	48/32/5	0.72 (0.53-0.98)	0.034	WW/WV+VV 21.88/22.34	0.564
MAP2K4: rs4791490	Rec.	145/86/5	48/30/7	0.22 (0.05-0.92)	0.039	WW+WV/VV 21.95/NA	NA
MEF2D: rs10159180	Dom.	62/123/51	33/34/18	1.44 (1.01-2.05)	0.041	WW/WV+VV 22.93/21.88	0.102
TNF: rs3093662	Dom.	203/30/3	79/6/0	1.54 (1.01-2.35)	0.046	WW/WV+VV 23.03/14.85	0.040
MEF2A: rs325383	Rec.	122/95/19	42/32/11	0.58 (0.34-0.99)	0.046	WW+WV/VV 21.52/34.66	0.143
MEF2D: rs16837408	Dom.	179/47/10	60/23/2	0.70 (0.49-0.99)	0.047	WW/WV+VV 19.09/37.95	0.027

Abbreviations: HR – Hazard Ratio, CI – Confidence Interval, Dom.-Dominant, Rec.-Recessive, Add.-Additive

*Adjusted for age, sex, smoking status, surgery, chemotherapy, radiation, chemoradiation, performance status, histology, and cancer stage

VITA

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