HHS Public Access

Author manuscript

Cancer Treat Res Commun. Author manuscript; available in PMC 2018 January 29.

Published in final edited form as:

Cancer Treat Res Commun. 2017 ; 10: 33–39. doi:10.1016/j.ctarc.2017.01.001.

Relationship between anti-depressant use and lung cancer survival

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Abstract

Objectives—In recent years, the anti-cancer properties of several commonly used drugs have been explored, with drugs such as aspirin and beta-blockers associated with improved cancer outcomes. Previous preclinical work demonstrated that tricyclic anti-depressants have antitumor efficacy in lung cancer. Our goal was to examine the association between anti-depressant use and survival in lung cancer.

Materials and Methods—We examined the association between use of common anti-depressants and survival in 1,097 lung cancer patients from the NCI-Maryland lung cancer study. The types of anti-depressants included in the study were norepinephrine and dopamine reuptake inhibitors, serotonin reuptake inhibitors, selective serotonin reuptake inhibitors, non-selective serotonin reuptake inhibitors, and tricyclic anti-depressants. Anti-depressant use was extracted from the medical history section of a detailed interviewer-administered questionnaire. Specific use in the three months before a lung cancer diagnosis was determined. Cox portioned hazards modeling was used to estimate the association between anti-depressant use with lung cancer-specific death with adjustment for potential confounding co-factors.

Results—Anti-depressant use was associated with extended lung cancer-specific survival. In an analysis of specific classes of anti-depressant use, NDRIs and TCAs were associated with improved survival. Importantly, the extended survival associated with anti-depressants was maintained after adjustment for the clinical indications for these drugs, suggestive of a direct effect on lung cancer biology.

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Conclusions—Considering the manageable and largely tolerable side effects of anti-depressants, and the low cost of these drugs, these results indicate that evaluation of anti-depressants as adjunct therapeutics with chemotherapy may have a translational effect for lung cancer patients.

Keywords

lung cancer; antidepressants; survival

Introduction

Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide.(1) The 5-year survival rate is approximately 15%. One of the major contributing factors to this dismal survival rate is the stage at which the majority of lung cancers are diagnosed—greater than 50% is diagnosed at stage 3 or 4, a time when both local and systemic treatments are unlikely to be curative. Although early detection of lung cancer among high-risk individuals can reduce lung cancer mortality by up to 20%,(2) there is still an immense need for the development of therapeutic approaches to help lung cancer patients worldwide.

Treatment options for lung cancer patients have recently progressed in the age of genomic medicine. For instance, targeted treatments for *EGFR* mutations and *EML4-ALK* rearrangements have extended survival times in advanced stage lung adenocarcinoma patients that carry these genomic alterations.(3) To complement ongoing efforts to improve the efficacy of chemotherapy and identify targeted therapies, the anti-cancer properties of several commonly used drugs have been explored in recent years; intriguingly, drugs such as aspirin and beta-blockers have been associated with improved cancer outcomes.(4-6) While these drugs can have toxicities, they are generally better tolerated than those associated with chemotherapeutic drugs and they can be easily combined with standard-of-care treatment.

Anti-depressants are commonly used in both the general population and cancer patients.(7) Previous studies have yielded contradictory results regarding possible links between the use of anti-depressants and cancer.(7-15) In lung cancer specifically, recent work in mice suggests that tricyclic anti-depressants could be an efficacious treatment strategy in small cell lung cancer and neuroendocrine tumors.(13) Based on these observations, we examined the relationship between anti-depressant use and prognosis in a population of patients diagnosed with lung cancer. We found that lung cancer patients taking NDRIs and TCAs have a significantly improved survival. These results may have significant translational impact for repositioning commonly used drugs as anti-cancer therapy.

Methods

Study population

We conducted a nested case-only analysis of patients with pathologically confirmed lung cancer, recruited from the greater metropolitan area of Baltimore, MD as part of the NCI-MD lung cancer case control study between 1998 and 2010. Written informed consent was obtained from all participants and the study was approved by the Institutional Review

Boards of all participating institutions. Inclusion criteria for this on-going case-control study have been previously described.(16) Briefly, participants were United States citizens, English-speaking and non-institutionalized. Participants took part in a detailed questionnaire at the time of their diagnosis that collected extensive information on nutrition, reproductive health, medical history, occupational history, smoking, and alcohol consumption. Never smokers were defined as those who smoked <100 cigarettes during their lifetime. Former smokers were defined as those who reported quitting smoking ≥1 year before the date of interview. Race was self-reported. A summary of the patient characteristics is shown in Table 1.

Extraction of medication use data

As part of the NCI-MD case controls study, patients took part in a questionnaire that gathered demographic, lifestyle and medical history. For this nested case-only study, we identified 1,097 lung cancer patients in the NCI-MD case control study with questionnaire data relating to medication use (Table 1). The health questionnaire was developed to include the assessment of medication use during the three months prior to interview. Patients were asked: Have you taken any prescription or non-prescription medications in the last 3 months? For those patients that responded yes, the name of the drug was recorded, later extracted and transcribed by hand. Anti-depressant use, including the reasons for its use, was also extracted. Anti-depressant drug classes considered in this analysis were: NDRIs (norepinephrine-dopamine reuptake inhibitors), SNRIs (serotonin and norepinephrine reuptake inhibitors), SSRIs (selective serotonin reuptake inhibitors), SRIs (serotonin reuptake inhibitor), NSSRIs (non-selective serotonin reuptake inhibitors), tricyclics (TCAs), and MAOIs (monoamine oxidase inhibitors). Patients were initially classified as having taken an anti-depressant if they reported using any of these drugs. Subsequently, variables were created to specifically document sole use of each anti-depressant class (Supplementary Table 1). A full list of the drugs within each class from this patient population is outlined in Supplementary Table 2.

Statistical Analysis

To test the magnitude of association between anti-depressant use with lung cancer-specific survival, 5-year lung cancer-specific hazard ratios (HR) were estimated using multivariable Cox proportional hazards regression modeling with adjustment for potential confounders, including age (continuous), sex (male/female), current smoking status (never/former/current), pack-years of smoking, race (African American/European American), histology (adenocarcinoma/squamous cell carcinoma/LCLC/other), stage (stage I/stage II/stage III/stage IV), income, education and drug indication. Survival times in the NCI/MD study were gathered through a query of the National Death Index (last entry 12/31/2012) and determined as time from diagnosis to last known follow-up or date of death. Time from lung cancer diagnosis was used to estimate the survival timescale, and failure was described as lung cancer-specific death. Proportional hazards assumptions were verified by visual inspection of log-log plots and using a nonzero slope test of the Schoenfeld residuals. In this study, causes of death other than lung cancer were censored (n=70). As competing risks are distinct from standard censoring, we performed a competing risks regression based on the

method of Fine and Gray (17) using the stcrreg function in STATA. A new variable was generated to specify the competing events (death from cancer and death from another cause).

We also addressed whether or not confounding by medication indication could have contributed to our observed findings. This is because the condition that the drug was initially prescribed for could be associated with lung cancer outcome also. Patients were asked why each drug was prescribed; this was then coded as a variable and included in the regression model. All statistical analyses were performed using STATA (*Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

Results

Characteristics of the study population

This study included 1,097 primary lung cancer cases (Table 1). The median age at diagnosis of the population was 65.8 years. Those taking anti-depressants were diagnosed earlier, more likely to be female, of European American ancestry and current smokers (Table 1). The overall median survival time across all stages was 2.7 years: for those not taking anti-depressants it was 2.6 years and for those who took anti-depressants the median survival was 3.2 years (Table 2). There were 382 patients with stage I lung cancer, 109 with stage II, 244 with stage III and 258 with stage IV; stage information was missing on 104 patients. As shown in Table 1, there were 59, 7, 118, 25, 4, 25, and 1 patients who reported taking NDRIs, SNRIs, SSRIs, SRIs, NSSRIs, TCAs, and MAOIs, respectively (overall, 207 patients reported taking anti-depressants). As there was only one patient that reported taking MAOIs, this patient was removed for single class analyses. Some of the patients in this study reported using more than one type of anti-depressant. The matrix of multiple anti-depressant use is outlined in Supplementary Table 1. The population examined is representative of the general population in the United States, in that the proportion of patients with lung cancer taking anti-depressants was similar to that observed in the general population.(18,19) As previously reported,(18,19) women were more likely to use anti-depressants than men (P=0.004).

Prolonged lung cancer survival associated with anti-depressant use

Overall, 19% (207) of the patients in this study had been prescribed one or more anti-depressants by their physician (Table 1 and Supplementary Table 1). One hundred and seventy-eight patients took a single anti-depressant and 29 patients took more than one (Table 1, Supplementary Table 1 and Supplementary Table 2). We found that, independent of the specific subclass, the administration of any anti-depressant was associated with a significantly prolonged survival (unadjusted model HR=0.68, 95% C.I. = 0.49 – 0.95, P=0.05, n=1,097) (Figure 1A) (Table 3).

In order to exclude potential bias in our results, we investigated the indication of anti-depressant administration in our cohort of patients. We found that predictors of anti-depressant prescription, such as the presence of comorbidities or pain management, were consistent with previous studies.(20) However, following adjustment for drug indication, and general potential confounders such as age, gender, stage, histology, race, smoking status and

pack-years of smoking in our model, anti-depressant use remained associated with a longer survival time (HR=0.68, 95% C.I. = 0.49 – 0.95, *P*=0.025) (Table 3) (Supplementary Table 4). Our model also included adjustment for metrics of SES including income and education level, as a proxy for insurance status. This was included in the analysis as patients who experience difficulty in paying for medications may be less likely to renew prescriptions. However, these variables did not modify the relationship between anti-depressant use and patient survival.

If patients not treated with anti-depressant drugs died of causes other than lung cancer early in the study, then those patients taking anti-depressants could appear to have an artificially reduced hazard of death. We therefore conducted a competing risks analysis to address this potential factor and found that the association between anti-depressant use and survival was not affected by censoring of the 70 individuals who died of causes other than lung cancer (fully adjusted model, HR: 0.68, 95% C.I. 0.50 – 0.91, *P*=0.012).

In addition, we also analyzed stage IV patients only, to remove some of the heterogeneity of the population. As shown in Supplementary Figure 1, the association between anti-depressant use and lung cancer specific survival remains in stage IV patients (HR: 0.60, 95% C.I. 0.41 – 0.89, *P*=0.011):

NDRI and tricyclic anti-depressants are associated with improved lung cancer survival

Anti-depressants comprise a heterogeneous group of drugs and mediate their effects through a range of neurotransmitters. To explore whether specific types of anti-depressants were associated with lung cancer survival or whether the group as a whole was associated with survival, we identified six classes of anti-depressants in the medical records of our patient cohort. We found that the administration of NDRIs (HR: 0.60, 95% C.I. = 0.39 – 0.92, *P*=0.018) and TCAs (HR: 0.57, 95% C.I. = 0.29 – 1.10, *P*=0.092) were associated with prolonged lung cancer survival, although the TCA results only approached statistical significance (Table 4).

As patients were sometimes treated with more than one kind of anti-depressant, we conducted an analysis of single anti-depressant class use. We again observed that patients who took only an NDRI (HR=0.56, 95% C.I. = 0.36 – 0.90, *P*=0.016 or tricyclic (HR=0.40, 95% C.I. = 0.18 – 0.91, *P*=0.028) had prolonged survival (Table 4) (Figure 1B and Figure 1C). We conducted a competing risks analysis and observed that survival was not affected by censoring of the 70 individuals who died of causes other than lung cancer (fully adjusted model NDRI, HR: 0.51, 95% C.I. 0.32 – 0.81, *P*=0.004) (fully adjusted model tricyclic, HR: 0.41, 95% C.I. 0.84 – 0.76, *P*=0.015).

Discussion

Cancer patients are three times more likely to develop major depression compared with the general population(7,21) and there is evidence that depression can contribute to adverse cancer outcomes.(7) Potential mechanisms include a potentially decreased likelihood to adhere to cancer treatments.(7) However, it is also possible that depression can have a pathophysiological effect via neuroendocrine or immunological signaling.(7) In this study,

we demonstrated that the administration of anti-depressants to lung cancer patients, particularly of the NDRI and TCA class, is associated with prolonged survival. While the relationship between treatment with TCAs and lung cancer survival was of borderline significance when TCA use was considered with other drugs (some patients who took TCAs were also treated with SSRIs, Supplementary Tables 1 and 2), we found that patients treated with only TCAs had a significantly better survival as compared with patients not treated with anti-depressants. As some patients that took TCAs also took other ant-depressants, this could explain that observation.

Our recent work in mouse models identified TCAs as potential agents for the treatment of lung cancer using an agnostic drug repositioning approach,(13) however a recent phase IIA clinical trial treating stage IV small cell lung cancer patients with the TCA desipramine recently ended due to a lack of efficacy and intolerance among most patients to the drug side effects. TCAs have high affinity for the histamine H1 receptor (H1R), the muscarinic acetylcholine receptor (mAchR), the 5-HT2 serotonin receptor (HTR2; and in particular HTR2a), and the α1-adrenergic receptor (ADRA1a and ADRA1b).(22-26) Interestingly, studies have detected these receptors on epithelial cancer cells.(13) Moreover, improved lung cancer survival among patients treated with beta-adrenergic receptor blockers was previously observed(6) while histamine agonists have also been linked to therapeutic response in breast cancer.(27) In lung cancer, TCAs induce cell death via histamine and adrenergic receptors by blocking $G\alpha_s$ and PKA, CREB and ATF1 signaling.(13) Additional studies have confirmed the induction of cell death by TCAs(10,28) while others found associations with reduced incidence of certain cancers.(29) Also, previous work on models of glioma showed a potential synergistic effect between chlorimipramine (a TCA) and dexamethasone,(11,30) while use of the TCA imipramine in combination with citalopram, an SSRI, induced apoptosis of acute myeloid leukemia cells.(31)

NDRIs were the other class of anti-depressant associated with survival. NDRIs mainly function by inhibiting the reuptake of dopamine and norepinephrine.(22,23) Recent studies have provided mechanistic evidence for a link between these neurotransmitters and cancer.(32-34) An agnostic screen of drugs that target cancer stem cells identified thioridazine(35-38)—an anti-psychotic drug that antagonizes dopamine receptors (specifically the DRD2 class)—as a potential anti-tumor drug that antagonizes VEGFR2/PI3K/mTOR signaling.(35-38) In addition, a recent compound library screen of the NCI-60 cell line repository identified the anti-psychotic trifluoperzine (TFP)—a DRD2 antagonist—as a potential anti-metastatic cancer drug.(12) In lung cancer, TFP inhibits the ß-catenin pathway and diminishes the stem-like phenotype.(39) It also reversed gefitinib-resistance. Functional dopamine receptors are expressed on ovarian, glioblastoma, and breast cancer stem cells.(36,38,40) Norepinephrine was recently shown to inhibit the migratory ability of pancreatic cells(41) while as mentioned earlier, beta-adrenergic receptor blockade is also associated with improved outcomes.(6,42-44) Recent work also found that the dopamine transporter inhibitor, sertraline, induced cell death in renal cell carcinoma,(45) data that collectively implicate catecholamine biology in carcinogenesis.(32,33)

Anti-depressants are widely prescribed for the treatment of conditions other than classical depression, including anxiety, circulatory disorders, insomnia and chronic pain management,

while some NRDIs—such as Bupropion—are used to aid smoking cessation. Mortality risk has been linked with smoking,(46,47) raising the possibility that the association between this drug with smoking cessation could confound the association between NDRI use and survival. However, in our population, smoking was not associated with survival (former versus never: HR 0.87, 95% C.I. 0.65-1.16) (current versus never: HR 0.91, 95% C.I. 0.69-1.21). In addition, we adjusted our model for smoking; therefore if the relationship between NDRIs and outcome was confounded by smoking cessation, we would have expected this to be reflected in the statistics. However, the association remained significant after the adjustment.

As mentioned, depression may be linked to cancer development.(48) In addition, anti-depressants are often prescribed to treat conditions other than psychological disorders. It was therefore important to determine whether our results were potentially confounded by drug indication. Our analysis found no association between the specific indication of prescribed anti-depressant and lung cancer outcome.

Interestingly, a recent study highlighted a relationship between anti-depressant use and cancer mortality. In a Danish cancer registry study, anti-depressant use--particularly in the 3-4 months before cancer diagnosis—was associated with an increased risk of mortality.(19) Former anti-depressant use was not associated with mortality. However, anti-depressant use was reported as a single group and therefore it is not possible to determine if our results are concordant with this recently published work. A clinical diagnosis of depression has previously been associated with poor outcomes in both breast and lung cancer(49,50); however it is not clear if, and how, anti-depressant use might have contributed to these observations. Of note, recent work has also highlighted the role of early palliative care in outcomes among patients with metastatic lung cancer. Specifically, patients with metastatic lung cancer that received early palliative care had a significant improvement in both quality of life and mood (51). Moreover, these patients received less aggressive care and also had a longer survival.

Our study has several limitations. Firstly, although we were able to ascertain whether patients took anti-depressants around the time of their diagnosis, we were not able to determine this prospectively, or determine the duration of use. Secondly, we do not have complete treatment data available for this cohort of patients and thus, it was not possible to look at potential drug interactions. Further studies will need to address whether the timing, dose and length of treatment can affect these outcomes. Patients in this study were diagnosed over a 12 year period: thus, given that lung cancer survival has incrementally increased over time(52) and that the prevalence of anti-depressant use varied over time, it is possible that there was a higher prevalence of anti-depressant use among the more recently diagnosed patients. We therefore assessed temporal trends in the prevalence of anti-depressant use during the period of study for this cohort. We found that there was no significant trend, either increasing or decreasing, among our population (Supplementary Figure 2), suggesting that this did not confound our results.

In summary, we have shown that lung cancer patients prescribed especially NDRIs and TCAs have prolonged survival. Although the mechanism of action is not completely clear,

evidence suggests that a direct physiologic mechanism of action involving neurotransmitter bioavailability and signaling might be involved.(13,32,33) The physiologic effects of stress and depression can affect neuroendocrine, immune, lymphatic and angiogenic responses, each of which could affect cancer progression.(32,33,53) However, depression may also affect how and when cancer patients interact with the medical system, meaning that an indirect mechanism cannot also be ruled out. Thus, further studies will be needed to assess the role of the sympathetic and parasympathetic nervous systems in carcinogenesis. In recent years, the re-positioning of commonly used FDA-approved drugs has garnered interest as a cost and time efficient strategy to uncover novel drugs for cancer treatment. In fact, considering that only a small percent of oncology drugs used in clinical trials attain FDA approval, and that anti-depressants are likely to be less toxic than traditional chemotherapeutic drugs, our insights suggest that further work should be done to understand the mechanism behind these drugs in the context of cancer and to investigate the safe use and repurposing of this drug class in cancer patients. We recognize that the study power is limited and while the results of this study need to be replicated and extended to a larger population size to include finer detail such as drug interactions, dose and duration of exposure, the association of TCA and other NDRI use with improved survival supports a movement towards repurposing existing drugs for lung cancer indication and may be relevant to other cancer types as well.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosure of Potential Conflicts of Interest and Funding Sources:

This work was supported by the Intramural Program of the Center for Cancer Research, National Cancer Institute (B.M.R., D.B., E.B., O.V.) and the Department of Defense (grant LC120252 to J.S.). The authors have no conflicts of interest to report.

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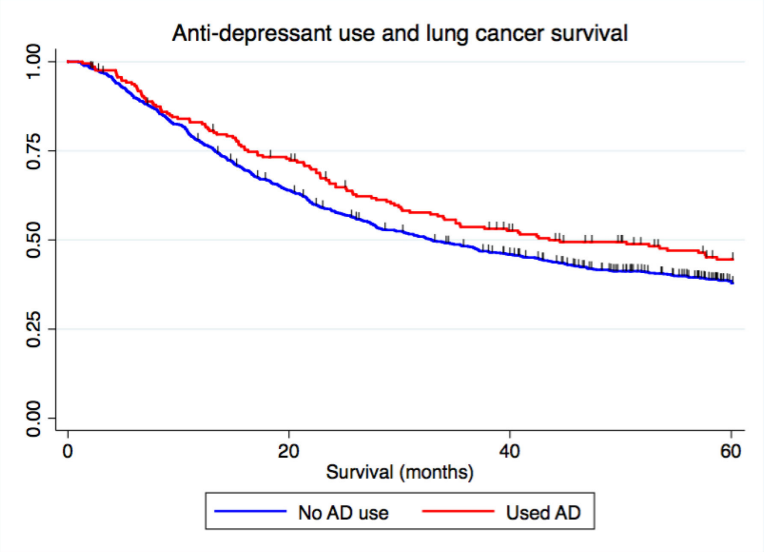
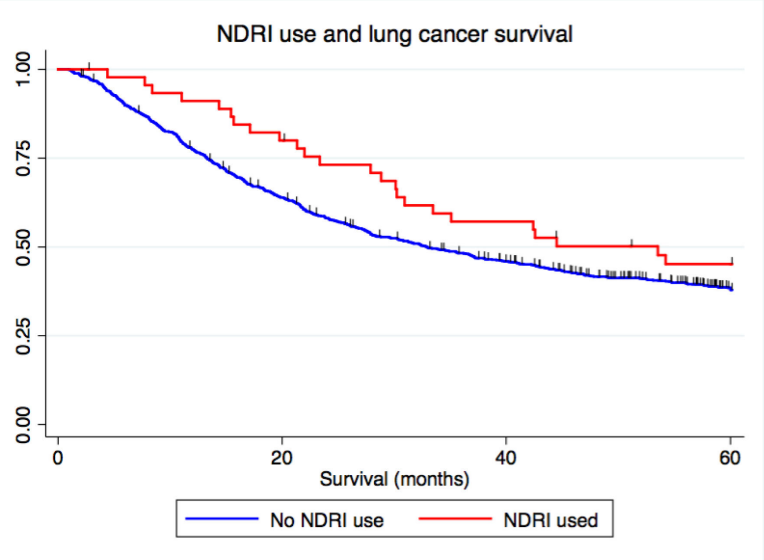
Microabstract

- Catecholamine signaling is increasingly recognized in connection with cancer
- The relationship between antidepressant use and survival was assessed in 1,097 lung cancer patients
- Antidepressants, which modulate catecholamines, are associated with lung cancer survival
- Of the six drug classes tested, TCAs and NDRIs are the main forms associated with outcome
- Both TCAs and NDRIs are associated with prolonged patient survival





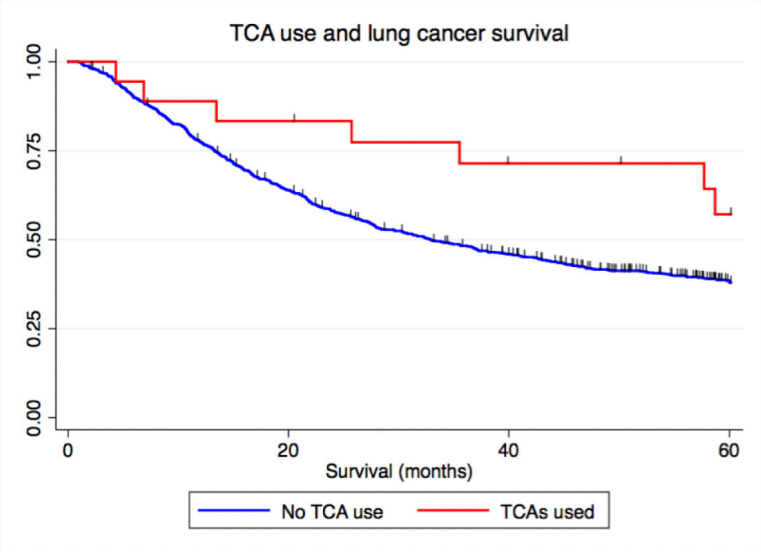


Figure 1.

Kaplan-Meier curves depicting the relationship between antidepressant use and lung cancer-specific survival. A) Overall antidepressant use and lung cancer-specific survival, B) NDRI sole use, and C) TCA sole use. NDRI denotes norepinephrine reuptake inhibitor, TCA denotes tricyclic antidepressant.

Table 1

Characteristics of the population

Characteristic	All	Not Taking Anti-depressants	Taking Anti-depressants	*P*
	1,097	890	207	
Age (mean ± S.D.)	65.8 ± 10.5	66.5 ± 10.4	63.0 ± 10.4	<0.001
Gender (%)				0.004
Male	560 (51%)	473 (53%)	87 (42%)	
Female	537 (49%)	417 (47%)	120 (58%)	
Missing	0	0	0	
Race (%)				<0.001
African American	312 (28%)	279 (31%)	33 (16%)	
European American	784 (71%)	611 (69%)	173 (84%)	
Unknown	1	0	1	
Smoking Status (%)				0.003
Never	89 (8%)	75 (8%)	14 (7%)	
Former	498 (45%)	423 (48%)	75 (36%)	
Current	510 (47%)	392 (44%)	118 (57%)	
Missing				
Pack-years (mean ± S.D.)	41.3 ± 30.0	40.9 ± 30.5	42.8 ± 27.6	0.408
Income				0.790
< $10,000	160 (15%)	131 (17%)	29 (16%)	
$10,000-$29,999	287 (26%)	236 (30%)	51 (28%)	
$30,000-$59,999	245 (22%)	203 (26%)	42 (23%)	
$60,000-$90,000	132 (12%)	102 (13%)	30 (17%)	
>$90,000	129 (12%)	102 (13%)	27 (15%)	
Missing	144 (13%)			
Education				0.029
5^{th} or 6^{th} Grade	24 (2%)	19 (2%)	5 (3%)	
7^{th}, 8^{th}, or 9^{th} Grade	143 (13%)	123 (14%)	20 (10%)	
10^{th} or 11^{th} Grade	128 (12%)	111 (13%)	17 (9%)	
12^{th} Grade	338 (31%)	272 (32%)	66 (33%)	
Some College	190 (17%)	141 (17%)	49 (25%)	
Technical School	43 (4%)	30 (4%	12 (6%)	
College	138 (13%)	118 (14%)	20 (10%)	
Professional School	48 (4%)	37 (4%)	11 (6%)	
Missing	46 (4%)			
Stage				0.251
I	382 (35%)	300 (34%)	82 (40%)	
II	109 (10%)	96 (11%)	13 (6%)	
III	244 (22%)	197 (22%)	47 (23%)	
IV	258 (24%)	211 (24%)	47 (23%)	

Characteristic	All	Not Taking Anti-depressants	Taking Anti-depressants	*P*
Missing	104	86	18	
Histology				0.626
Adenocarcinoma	504 (46%)	399 (45%)	105 (51%)	
Squamous cell carcinoma	279 (26%)	229 (26%)	50 (24%)	
Large cell carcinoma	24 (2%)	20 (2%)	4 (2%)	
Other*	280 (26%)	234 (26%)	46 (22%)	
Missing	10	8	2	
Survival (median years, I.Q.R.)				
Overall Survival	2.7, 0.5-5.0	2.59, 0.5-5.0	3.2, 0.6-5.0	
Lung Cancer Deaths	647	537	110	
All Deaths	698	576	122	

S.D. denotes standard deviation, I.Q.R. denotes interquartile range

*Includes designation NSCLC and SCLC

Table 2

Distribution of use by anti-depressant drug class

	N	N
Drug Class	**(no exclusions)**	**(excluding other anti-depressant drugs)**
NDRI	59	46
SNRI	7	5
SSRI	118	93
SRI	25	12
NSSRI	4	3
Tricyclic	25	18
MAOI	1	1

NDRIs (norepin ephrine-dopamine r euptake inhibitors),

SNRIs (serotonin and norepinephrine reuptake inhibitors) SSRIs (selective serotonin reuptake inhibitors)

SRIs (serotonin reuptake inhibitor)

NSSRIs (non-selective serotonin reuptake inhibitors)

tricyclics and MAOIs (monoamine oxidase inhibitors)

Table 3

Association between anti-depressant use and lung cancer survival

	Univariable			Multivariable*		
	HR	**95% (C.I.)**	***P***	**HR**	**95% (C.I.)**	***P***
Not taking anti-depressants	1	Reference		1	Reference	
Taking anti-depressants	0.68	0.49 – 0.95	0.052	0.68	0.49 - 0.95	0.025

HR denotes hazard ratio; C .I. de notes confidence interval

*denotes adjustment for age, race, gender, smoking status, pack-years of smoking, race, stage, histology, income, education level and drug indication

Table 4

Association between class of anti-depressant use and lung cancer survival

	HR	95% (C.I.)	*P*	HR	95% (C.I.)	*P*
	Mixed Class Use			**Single Class Use**		
No anti-depressant use	1	Reference		1	Reference	
NDRI	0.54	0.33 - 0.88	0.014	0.52	0.31 - 0.89	0.017
SNRI	1.39	0.53 – 3.68	0.498	1.63	0.56 – 4.78	0.374
SSRI	0.77	0.49 – 1.21	0.260	0.72	0.45 – 1.17	0.185
SRI	1.77	0.93 - 3.36	0.080	1.54	0.65 - 3.64	0.329
NSSRI	1.87	0.55 – 6.36	0.312	2.21	0.51 – 9.61	0.289
Tricyclic	0.58	0.29 – 1.13	0.107	0.40	0.17 – 0.92	0.031

HR denotes hazard ratio; C.I. denotes confidence interval

P denotes adjustment for age, race, gender, smoking status, pack-years of smoking, race, stage, histology, income, education level and drug indication