METFORMIN & NON-SMALL CELL LUNG CANCER AMONG SEER-MEDICARE BENEFICIARIES: ANALYSIS OF COST, OUTCOMES & UTILIZATION

by

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A dissertation submitted to the faculty of
The University of North Carolina at Charlotte
in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in
Health Services Research

Charlotte

2017

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ABSTRACT

CYNTHIYA RUBAN. Metformin & Non-Small Cell Lung Cancer Among Seer-Medicare Beneficiaries: Analysis of Cost, Outcomes & Utilization. (Under the direction of DR. CHRISTOPHER BLANCHETTE)

Type 2 diabetes (T2D) and non-small cell lung cancer (NSCLC) each represent costly chronic diseases with substantial public health implications. A better understanding of the relationship between T2D treatments and NSCLC has many important implications for prevention and management. There are several classes of antidiabetic drug medications (ADM), however this analysis will focus on metformin, which is a part of the biguanide drug class and generally first line therapy for T2D. This thesis is comprised of three studies that will utilize the Surveillance, Epidemiology, and End Results (SEER) Medicare database from 2007 to 2013 for NSCLC patients.

The first study investigated the cost and utilization of diabetes patients with NSCLC. The adjusted analysis was performed using quantile regression for healthcare costs and a negative binomial model for healthcare utilization. Healthcare costs and utilization was higher in various healthcare settings for diabetic NSCLC patients compared to NSCLC Patients and increased with cancer stage.

The second study measured the time to incident NSCLC diagnosis for metformin versus other antidiabetic drug medication (Thiazolidinedione, Sulfonylurea, Dipeptidyl peptidase-4 inhibitor). Kaplan-Meier method and log-rank tests were used to examine overall survival (time from incident medication to NSCLC diagnosis) for metformin and other antidiabetic drug medication users. Multivariable cox proportional hazards models were fit to assess the risk of NSCLC after incident medication utilization. Diabetic NSCLC patients with incident metformin had a significantly longer time to NSCLC diagnosis than NSCLC patients on other antidiabetic drug medication, prior to adjusting for covariates.

The third study assessed the effect of metformin exposure on survival among patients with NSCLC diagnosis. Kaplan-Meier survival analysis was used to examine overall survival of metformin and other antidiabetic drug medication. NSCLC patients with incident metformin use, prior to and after NSCLC diagnosis did differ on survival compared to patients on other antidiabetic drug medications.

The results from these three studies add to the body of literature on metformin and lung cancer. While findings did not support an effect on mortality, a delay in diagnosis was identified. While Aim 3 lacked statistical significance and the effect size was not meaningful, it has contributed a greater understanding of the association of metformin in NSCLC patients. Implications of study findings support the need for further exploration of the relationship between metformin and lung cancer.

DEDICATION

To my parents, thank you for your words of encouragement & motivation.

To my husband, thank you for your love, your patience, & your faith.

To my brother, thank you for always believing in me.

ACKNOWLEDGMENTS

A dissertation is not the outcome of the efforts of entirely one individual. Many people have contributed to its development. I would like to take the opportunity to acknowledge those who have made some impact on my doctoral journey.

First and foremost, I would like to thank my advisor Dr. Christopher Blanchette. I appreciate all his contributions of time, ideas, and funding to make my doctoral experience stimulating and productive. I am thankful to have him as my committee chair, for his mentorship, words of wisdom, encouragement, and most of all patience throughout the entire process.

Thank you, Dr. William Saunders, for his mentorship, guidance and being a part of my dissertation committee. Over the past three years he has provided advice, mentorship, and encouragement many times during my graduate school career. I wish to thank my committee members who were more than generous with their expertise and time, Dr. Joseph Marino, Dr. Marc Kowalkowski, and Dr. Reuben Howden. Each of you has given of your time, expertise, and energy and I am richer for it.

This journey would not have been possible without the support of my family, professors and mentors, and friends. To my parents, thank you for encouraging me in all of my pursuits and inspiring me to follow my dreams. To my brother, thank you for words of wisdom and consistently inspiring me. To my friends, thank you for listening, offering me advice, and supporting me through this entire process.

Finally, and most importantly, I would like to thank my husband. Thank you for supporting me throughout this process and constantly encouraging me when the tasks seemed arduous and insurmountable.

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LIST OF ABBREVIATIONS

ADM	Antidiabetic Medication
CDC	Centers for Disease Control
ER/ED	Emergency Room
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD -O	International Classification of Diseases for Oncology
MEDPAR	Medicare Provider Analysis and Review File
NCH	Medicare Carrier Claims File (old name, physician/supplier)
NDC	National Drug Code
NSCLC	Non-Small Cell Lung Cancer
OUTP	Medicare Outpatient File
PDE	Part D Event File
PEDSF	Patient Entitlement and Diagnosis Summary File
PPPM	Per Person Per Month
SEER	Surveillance, Epidemiology, and End Results Program
T2D	Type 2 Diabetes

Chapter 1: Introduction

Cancer is the second leading cause of death worldwide, and mechanisms involved in the relationship between type 2 diabetes (T2D) and cancer are not completely understood, and even less is known about the association with non-small cell lung cancer (NSCLC) (Masters, 2015). However, there is a likely association with hyperinsulinemia, which is a result of insulin resistance characteristic of T2D (Tarver, 2012). Insulin's role in cell proliferation, as well as repression of apoptosis, could play a vital role in the development of cancerous tissues (Hundal, 2000). Although these systemic responses are reasonably well understood, the current literature does not adequately explain organ-specific cancer risk.

Lung cancer starts when cells located in the lung become abnormal and begin to grow out of control (Masters, 2015). As an increased number of cancer cells develop, they can form into a tumor and spread to other areas of the body (Masters, 2015). There are two types of lung cancer: small cell lung cancer (accounts for 10- 15% of all lung cancer diagnosis) and non-small cell lung cancer (NSCLC) (accounts for 85 - 90% of all lung cancer diagnosis) (Masters, 2015).

Lung cancer is the second most commonly diagnosed cancer in men and women. An estimated 224,390 new cases of lung cancer are expected in 2016, accounting for about 14% of all cancer diagnoses (Siegel, 2015). The incidence rate has been diminishing in the United States since the mid-1980s in men, but only since the mid-2000s in women (Tarver, 2012). From 2007 to 2011, lung cancer incidence rates declined by 3.0% per year in men and by 2.2% per year in women (Siegel, 2015). It is estimated that 221,200 new cases of lung cancer are expected in 2015, accounting for about 13% of all cancer diagnoses (Tarver, 2012). Lung cancer accounts for more deaths than any other cancer in both men and women. An estimated 158,080 deaths are expected to occur in 2016, accounting for about 1 in 4 cancer deaths. The 5-year survival rate for small cell lung cancer (7%) is lower than that for NSCLC (21%) (Tarver, 2012).

Improvement of glucose control remains one of the central goals of effective diabetes management, which aims to reduce morbidity and mortality by decreasing the risk of diabetes-

associated complications (Tarver, 2012). A vast number of factors are considered by clinicians and patients when selecting adequate pharmacologic diabetes therapies. Various classes of diabetes drugs operate at different parts of this glucose–insulin pathway. This may include increases in insulin secreted by the pancreas, increases of the sensitivity to insulin by target organs, and decrease the rate at which glucose is absorbed by the gastrointestinal tract (Kahn, 2005).

Metformin is a part of the biguanide class of oral hypoglycemic agents and is a regularly prescribed medication for various conditions including diabetes, polycystic ovary syndrome (Nestler, 2008) and non-alcoholic fatty liver disease (Marchesini, 2005). For T2D, it is the first-line drug of choice among patients with normal kidney function (Nathan, 2009). The primary mechanism of operation is thought to be primarily via decreased hepatic glucose output by inhibition of gluconeogenesis, with a secondary drop in insulin levels, with no major effects on insulin signaling. Furthermore, an 'average' individual with T2D has three times the normal rate of gluconeogenesis, thus, metformin treatment reduces this by more than one-third (Hundal, 2000).

Currently, there is no known effective preventive strategy for lung cancer, except for smoking cessation. Studies that have assessed the impact of T2D on NSCLC have yielded variable results (Govindarajan, 2007; Bodmer, 2012). Given the strong in-vivo and in-vitro evidence of a potential protective effect of metformin (Marchesini, 2005; Nathan, 2009; Hundal, 2000), as well as support of the concept from other malignancies (Raval, 2016; Soffer, 2015), a larger population based study is essential. This study will investigate the cost and utilization of diabetes patients with Non-Small Cell Lung Cancer, measure the time to incident Non-Small Cell Lung Cancer diagnosis for metformin versus other antidiabetic drug medication and assess the effect of metformin exposure on survival among patients with Non-Small Cell Lung Cancer diagnosis.

Chapter 2: Literature Review

Cancer in the US

Cancer impacts the lives of over 11 million Americans, and it does not discriminate by age, ethnicity, income or region (www.srab.cancer.gov). Since the beginning of this century, the overall incidence and death rates of cancer have been decreasing. This is the result of early detection, cancer prevention, and better treatment options. In the annual report to the nation on the status of cancer, 1975- 2007, Kohler and colleagues found a decrease in the overall incidence of cancer in the U.S. population. However, due to the expected increase in life expectancy, the absolute number of individuals diagnosed with cancer is projected to increase creating an increase in demand for cancer-related health care services (Kohler, 2011). The authors demonstrate the need for effective management of cancer through not only prevention, detection treatment, and survivorship but also providing resources necessary to provide quality care. The authors conclude that utilization of quality population-based data systems and translating evidence-based clinical as well as basic research findings are imperative to make sound public policy decisions for cancer.

Through utilization of patient-reported demographic and socioeconomic data from the Social and Economic Supplement Clegg and colleagues (2009) reported cancer-related disparities linked to individual-level socioeconomic status for all combined cancers as well as the specific cancers of lung, breast, prostate, cervix, and melanoma (Clegg, 2009). Results showed, for each of the major cancer diagnoses, significant differences in incidence rates from self-reported data of education level, family income, and poverty status. The authors note the importance of differentiating between patient-level characteristics and community level characteristics, particularly if measuring a similar construct such as socioeconomic status. They conclude that social disparities in cancer incidence may be related to socioeconomic and demographic differences in cancer-related risk factors and behaviors. Moreover, disparities in health care access may contribute to different types and stages of care and individuals with lower SES and educational level are more likely to have higher rates of cancer risk factors.

The American Society of Clinical Oncology, Meropol and colleagues (2009) issued a guidance statement regarding the cost of cancer care. The statement recognizes that while better prevention, detection, and treatment have reduced the cancer death rate, costs of cancer treatment have steadily risen and continue to grow rapidly creating an unsustainable financial burden on all levels of cancer care. The guidance statement makes the following recommendations: recognizes that physician-patient discussions regarding the cost of care are an important, a need for communication support tools for oncology providers related to the cost of care, the development of educational resources about the high cost of cancer care. This article identifies the need for a clear understanding of cost drivers in the cancer care system, so that all patients can get access to and can afford high quality cancer care.

Lung Cancer

Lung cancer is the principal cause of cancer mortality worldwide, accounting for approximately 1.3 million deaths each year. The 5-year relative survival rate for patients from 1995 to 2001 with lung cancer was 15.7%. The 5-year relative survival rate ranges depending on the stage at diagnosis, from 49% to 16% to 2% for patients with local, regional, and distant stage disease, respectively (Ries, 2005)

NSCLC is any lung cancer, not inclusive of small cell lung cancer (SCLC) (Peters, 2012). The most prevalent types of NSCLC are adenocarcinoma, squamous cell carcinoma and large cell carcinoma (Peters, 2012). However, there are many other types of lung cancer that occur less commonly, and can occur in unusual histologic variants. Nevertheless, NSCLCs is correlated with cigarette smoke, however adenocarcinomas can be observed in patients who have never smoked (Peters, 2012). Some patients with resectable NSCLC may be treated with surgery or surgery accompanied by chemotherapy (Peters, 2012). In unresectable cancer, a localized control may be achieved through radiation therapy in many patients (Masters, 2015). However, a cure is seen only in a small subset of patients. Patients with advanced unresectable NSCLC can achieve long-term survival with radiation therapy in combination with immunotherapy.

There are four stages of NSCLC. Stage I NSCLC is cancer which is only located in the lungs and it has not spread to any of the lymph nodes (Edge, 2015). Stage II is when cancer has spread to the lymph nodes that are nearby (Edge, 2015). Stage III is NSCLC that may be found within the lungs, lymph nodes and the middle of the chest; this is an advanced form of cancer. Finally, stage IV is the most advanced form of NSCLC and characterized by the spread of cancer into both lungs and to the area around the lungs and/or other parts of the body (Edge, 2015).

Cipriano and colleagues (2011) assessed the cost of cancer treatment, including costs that were the patient's responsibility from 1992 – 1993. 60, 231 lung cancer patients were identified in the SEER Medicare data. The first six months of health care costs after diagnosis ranged from $2,687 (no active treatment) to $9,360 (chemo-radiotherapy). Variation occurred by stage at diagnosis as well as histologic type.

Diabetes and Cancer

One of the fastest growing epidemics, not only in the United States, but worldwide is T2D. The International Diabetes Federation estimated that diabetes will affect 552 million people worldwide by 2030. The Centers for Disease Control and Prevention (CDC) (2014) estimates that greater than 25.8 million Americans (8.3% of the population) has diabetes. The CDC also estimates that of these individuals approximately 7 million are undiagnosed and are therefore untreated. T2D accounts for 90%-95% of diagnosed diabetes cases in the United States, and has been widely attributed to an increase in obesity (CDC, 2014). It is estimated that nearly one third of the US population is obese (CDC, 2014). The rates of growth in obesity and diabetes have mirrored each other over the past 2 decades (CDC, 2014). The complications of diabetes, which are comprised of kidney disease, heart disease, blindness, and increased risk for amputations, are as serious as they are diverse (CDC, 2014).

There is increasing evidence linking metformin use to decreased cancer risk and improved outcomes (Marchesini, 2005; Nathan, 2009; Hundal, 2000). Metformin may influence cancer cells through indirect (insulin-related) effects, or by directly influencing cancer cell

proliferation and apoptosis (Hadad, 2008). Metformin's suggested mechanism of action in preventing cancer is via the AMPK pathway (Hadad, 2008). AMPK is a cellular fuel sensor pathway sensitive to heightened AMP/ATP ratio. Once activated, AMPK phosphorylates and inactivates various metabolic enzymes included in ATP-consuming cellular events such as fatty acid and protein synthesis connecting the acetyl-coenzyme A carboxylase (Kahn, 2005). Furthermore, AMPK activation within cancer cells has been shown to inhibit the mTORC1 pathway and S6K1 phosphorylation (via the TSC complex) implicated in protein synthesis (Kahn, 2005). Metformin also activates the AMPK pathway in the liver causing decreased gluconeogenesis, which leads to a decrease in insulin levels (Kahn, 2005). This indirectly leads to decreased action of insulin on cancer cells, which inhibits the mTOR pathway. Ergo, metformin has two actions on this axis (reducing stimulation of the insulin receptor and reducing signaling through the mTOR pathway) thereby reducing the end effects of mTOR signaling (Pollak, 2010).

Metformin may also be related with the regulation of autophagy (Tomic, 2015), "a catabolic process of degradation of cytoplasmic components within lysosomes," (Mizushima, 2007). Autophagy is considered a survival mechanism as the result of in hostile conditions to maintain cell integrity, however paradoxically, it also involves a particular mode of cell death called autophagic cell death (Buzzai, 2007). Previous work suggests that metformin induces autophagy in cancer cells (Tomic, 2015; Buzzai, 2007). In summary, there is strong in vitro evidence metformin may influence cancer cells. Metformin may work directly on the AMPK pathway, preventing apoptosis or regulating autophagy.

The association of metformin and specific malignancies has been assessed in previous studies. In a study conducted by Raval et al (2016) analyzed a cohort study of elderly men (older than 66 years) with incident prostate cancer and preexisting diabetes. Results from this study indicated a significantly fewer metformin users were diagnosed with advanced prostate cancer than nonusers (4.7% versus 6.7%, $p < 0.03$), prior to adjustment. After adjusting for other

independent variables and observed selection bias, metformin use was associated with a 32% reduction in the risk of advanced prostate cancer. A similar protective effect was documented in a study by Soffer and colleagues (2015). Metformin monotherapy and combination therapy was assessed in breast, endometrial, and ovarian cancer risk, and the composite cancer risk. Results from this study demonstrated that women who used metformin combination regimens versus metformin only had a 15% lower breast cancer risk (adjusted HR=0.85, 95% CI 0.69 to 1.04). Likewise, in a study by Spillane (2014) colorectal patients with metformin exposure was identified. While there were no statistically significant association between metformin exposure and colorectal cancer at diagnosis, it appeared that high intensity utilization of only metformin use (OR = 0.52, 95% CI 0.25–1.10) may be associated with reduced odds of disease.

Various meta-analyses have also been conducted that assess the association between cancer and metformin. Bowker et al (2006) conducted a population-based cohort study using administrative databases from Saskatchewan Health. Cancer-related mortality was compared among inception cohorts of metformin users and sulfonylurea monotherapy users. Authors identified 10,309 new users of metformin or sulfonylureas with an average follow-up of 5.4 years. Cancer-related mortality during the follow-up was 3.5% for metformin users, 4.9% sulfonylurea monotherapy users, and 5.8% for subjects who used insulin. Upon multivariate adjustment, the sulfonylurea cohort had greater cancer-related mortality compared with the metformin cohort (adjusted HR 1.3). Conversely, insulin use was associated with an adjusted HR of cancer-related mortality of 1.9. Findings from this study indicate that Patients with T2D exposed to sulfonylureas and exogenous insulin had a significantly heightened risk of cancer-related mortality related with patients exposed to metformin. However, there is uncertainty if this increased risk is related to a protective effect of metformin or a harmful effect of sulfonylurea and insulin.

In this meta-analysis, there is strong in vitro evidence metformin may impact cancer cells. Metformin may work directly through its effect on the AMPK pathway, preventing

apoptosis or regulating autophagy. It may also have indirect effects through lowering insulin levels. Even with these limitations, epidemiologic data are accumulating, and metformin use seems to be associated with decreased cancer risk and possibly improved outcome.

In a study by Farmer et al. (2016) authors conducted a systematic review of the association between metformin and overall or site specific cancer in patients with T2D. For all cancer sites, 16 of 46 studies estimated a protective effect of metformin, however, 10 of 16 studies had an upper confidence limit below 1. Among the reviewed studies, there was significant variation in study design and observed risk reduction (from 0.04% to 77% reduction in risk). Of those least affected by bias (defined by 8 domains: (outcome, exposure, baseline confounding, control selection, censoring methods, immortal time, missing data, time-dependent confounding), there was limited support for a causal effect of metformin on reduced cancer risk. However, in this meta-analysis all but two studies were retrospective, and therefore results should be interpreted with caution.

Most studies to date have been observational which is problematic as there may be presence of potential selection bias. Metformin users tend to be different than non-metformin users in terms of stage of diabetes and baseline risk of cancer. Metformin use in general is that metformin-treated patients may have different clinical characteristics than other diabetes-related treatment groups. While some studies adjusted for these confounders, thus minimizing the potential bias, some secondary data sources are limited by the inability to measure these confounders or unmeasured confounding may remain even when accounted for. Another limitation the comparator group needs to be considered. In some studies, a comparator group of diet, as opposed to no metformin, made metformin appear more protective, conversely using other antidiabetic medication or less metformin as a reference group made metformin appear less protective. Finally, only few studies demonstrated a dose-response relationship between lung cancer and diabetes to support biological plausibility.

Even with these limitations, epidemiologic data are accruing and metformin use appears to be associated with decreased cancer risk and possibly enhanced outcomes. The most compelling evidence is in endometrial cancer, and has led to a current University of Texas MD Anderson Cancer Center sponsored study of metformin and/or a program called "lifestyle intervention" on the endometrium in post-menopausal obese women (M.D. Anderson Cancer Center, 2017).

Diabetes and Non-Small Cell Lung Cancer

When examining the association of metformin use with NSCLC outcomes it is essential to take into consideration all aspects of the diabetes diagnosis. As previously mentioned, contrary to other malignancies, population-based studies suggest that the risk of NSCLC may have an inverse relationship with diabetes. Several studies have assessed the risk of lung cancer, some of which indicate that metformin, may be chemopreventive in patients with T2D (Govindarajan, 2007; Lai, 2012; Ruiter, 2012), whereas other studies show no beneficial effect (Bodmer, 2012; Mazzone, 2012). Likewise, some studies suggest that sulfonylureas and insulin may promote increased risk of lung cancer (Chang, 2012; Hsieh, 2012), conversely, others show no harmful effects (Lai, 2012; Gu, 2013). As the biologic association of the suspected relationship it is still uncertain, as the debate continues concerning the association between diabetes and NSCLC.

In a meta-analysis conducted by Wan and colleagues (2016) a comprehensive analysis produced 17 individual studies from 10 publications. Findings revealed a significant association of metformin use with a better survival of lung cancer patients with diabetes (for disease free survival (DFS): HR = 0.65, 95%CI = 0.52-0.83; for OS: HR = 0.78, 95%CI = 0.64-0.93). Stratified results also indicated similar results in non-small cell lung cancer (for DFS: HR = 0.70, 95%CI = 0.51-0.96; for overall survival(OS): HR = 0.75, 95%CI = 0.58- 0.97) and a reduction in the risk of cancer-related mortality in patients receiving chemotherapy (for DFS: HR = 0.71, 95%CI = 0.64-0.83; for OS: HR= 0.58, 95%CI = 0.47-0.71). Similarly, Zhang et al. (2014) summarized lung cancer and diabetes studies from 2009–2013 and explored the rationale of

heterogeneity. Metformin therapy was associated with significantly lower risks of lung cancers (4 studies; pooled relative risk = 0.71, 95% confidence interval (CI): 0.55, 0.95; P = 0.02). However, authors documented that a major source of heterogeneity was adjustment of smoking status and cancer site. Conversely, in a Meta-analysis of cohort studies by Zhu et al. (2016) was utilized to derive an accurate estimate of the role of T2D in lung cancer. Authors employed Medline and Embase for eligible articles to October 2015. Findings from this study indicate a significant correlation between T2D and poor survival in lung cancer patients, especially in the subgroup of surgically treated NSCLC patients (Zhu, 2016).

Despite findings of these two meta-analysis (Wan, 2016; Zhang, 2014) similar epidemiological limitations are present when assessing the association of NSCLC and diabetes to cancer and diabetes. Firstly, while some confounders were addressed, there remains variation in the findings across these studies. Moreover, there could be residual or unknown confounders that have not been accounted for. Second, lack of adjustment of smoking status can vastly attenuate the association, and thus results from these studies should be interpreted cautiously. Third, immortal time bias, a type of bias associated with temporal sequencing and time on the exposure-outcome, may exaggerated the association. Future studies should take into consideration these factors and assess the dose response nature of antidiabetic medication.

In summary, data suggest that specific ADM lower risk of NSCLC, but the literature is inconclusive, and there are still several questions left to answer. Previously reported drug-cancer associations may be explained by the fact that antihyperglycemic medications are associated with cancer risk factors, therefore may be confounding by unmeasured risk factors. A limited number of studies have examined factors that may impact the biologic plausibility of these associations, such as the duration, dose, or frequency of medication use. Some diabetes medications have only recently been approved for use (i.e. insulin analogs, incretin-based therapies). Therefore, studies of these agents will have limited follow up time to evaluate general cancer occurrence beyond the risk assessed in high-dose animal model studies.

Research Aims

Diabetes has been frequently associated with increased risk of several highly prevalent cancers, but for many, including NSCLC, more research is vital. Moreover, it is not clear whether cancer risk is influenced by duration of diabetes. This is a critical and complex issue which may be further complicated by the multidrug therapy often necessary for diabetes treatment. To adequately address these gaps in the literature this dissertation is comprised of three studies to explore the relationship between metformin and NSCLC.

Aim 1: To describe the cost and utilization of diabetes patients with Non-Small Cell Lung Cancer.

Aim 2: To measure the association between incident metformin exposure and Non-Small Cell Lung Cancer diagnosis, among diabetic patients.

Aim 3: To measure the association between metformin exposure and survival among diabetic patients with Non-Small Cell Lung Cancer.

Chapter 3: Investigation of the cost and utilization for diabetes patients with Non-Small Cell Lung Cancer

Introduction

Cancer is the second leading cause of death worldwide, and mechanisms involved in the relationship between Type 2 Diabetes (T2D) and cancer are not completely understood, and even less is known about the association with non-small cell lung cancer (NSCLC). However, there is a likely association with hyperinsulinemia, which is a result of insulin resistance characteristic of T2D (Tarver, 2012). Insulin's role in cell proliferation, as well as repression of apoptosis, could play a vital role in the development of cancerous tissues (Hundal, 2000). Although these systemic responses are reasonably well understood, the current literature does not adequately explain organ-specific cancer risk.

There is increasing evidence linking metformin use to decreased cancer risk and improved outcomes (Marchesini, 2005; Nathan, 2009; Hundal, 2000). Metformin may influence cancer cells through indirect (insulin-related) effects, or by directly influencing cancer cell proliferation and apoptosis (Hadad, 2008). Metformin's suggested mechanism of action in preventing cancer is via the AMPK pathway (Hadad, 2008). AMPK is a cellular fuel sensor pathway sensitive to heightened AMP/ATP ratio. AMPK activation within cancer cells has been shown to inhibit the mTORC1 pathway and S6K1 phosphorylation (via the TSC complex) implicated in protein synthesis (Kahn, 2005). Metformin also activates the AMPK pathway in the liver causing decreased gluconeogenesis, which leads to a decrease in insulin levels (Kahn, 2005). This indirectly leads to decreased action of insulin on cancer cells, which inhibits the mTOR pathway. Ergo, metformin has two actions on this axis (reducing stimulation of the insulin receptor and reducing signaling through the mTOR pathway) thereby reducing the end effects of mTOR signaling (Pollak, 2010).

There are few retrospective studies (Lang, 2009; Fox, 2008, Woodward, 2007) that have estimated the cost of lung cancer in the US, these studies employed varied designs and methods

however, they did not analyze cost components by type of service or setting and specifically within diabetic patients. Resource use and costs among patients with lung cancer overall and by service setting may help inform decision-making about the ideal distribution of healthcare resources. Ergo, the objective of this study was to assess the cost and utilization of diabetic patients with non-small cell lung cancer.

Methods

Data Source

This is a retrospective database study of linked SEER cancer registry data and Medicare claims. The SEER – Medicare linked databases provided a temporal view of patients with T2D and NSCLC (2007 - 2013). The SEER program collects information on incident cancer diagnosis within a set of defined geographic areas (Warren, 2002). The program originated in 1973, now includes registries that cover about 26 percent of the U.S. population (Warren, 2002). There is vast information captured in the database including patient's age, race, sex, and marital status. Information about cancer includes the month and year of diagnosis, behavior, the site, and stage. Moreover, there is also staging information in the SEER data which is based on a classification that can vary by cancer site as well as year of diagnosis (Warren, 2002).

Study Population

Cases and controls were included in the study if they were diagnosed with NSCLC between January 01, 2008 and December 31, 2013, at least 66 years old, continuous enrollment in Medicare A and B in the 12 months prior to diagnosis. Patients were excluded if their date of death recorded was prior to or in the same month of diagnosis and if they were enrolled in an HMO at any time during the 12 months prior to diagnosis, as complete claims for these patients were unavailable.

NSCLC diagnosis was based on the International Classification of Disease for Oncology (3rd edition, ICD-O-3) histology codes in the SEER Medicare data. Tumor stage was classified according to the 6th edition of the American Joint Commission on Cancer. Controls were patients

with NSCLC without prevalent diabetes, prior to NSCLC diagnosis. Cases were defined as patients with a diagnosis of preexisting T2D in NSCLC patients identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) 250.xx prior to cancer diagnosis utilizing Medicare claims files. T2D NSCLC patients must have had at least 2 claims in the 12 months prior to NSCLC diagnosis.

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical characteristics for both groups. Differences between groups were assessed using Chi-square test for categorical and t-tests for continuous variables. We assessed healthcare cost and claims for diabetes and Non-diabetes patients stratified by stage of NSCLC. Healthcare claims and costs were examined by the healthcare setting in which they happened and represent the claims for services incurred within a specific location. Healthcare costs and claims for utilization were reported by person-month due to variable follow-up.

The total number of person-months was calculated for all patients that were alive and were diagnosed with NSCLC across the study period. Total healthcare cost and service claims were summed across the study period and divided by person-months. Cost data represented the actual paid (amount reimbursed by Medicare) amounts for healthcare services.

The analysis was performed adjusting for demographic (age, sex, race) and clinical (comorbidity score) factors using a negative binomial model for count of healthcare events and quantile regression for healthcare costs. Healthcare costs and utilization was segmented by month using Lin's method, a methodological weighting approach in which the post-period is divided into segments of time and then each segment is assessed for effect with the observable sample after which the effect is averaged across the follow-up time (Lin, 1997). The cumulative cost (2016 dollars) for each 30-day period, for an observation was summed for each interval and quantile regression was used to estimate the median (0.5) conditional quantile of healthcare cost within that interval while adjusting for potential confounding variables. The quantile regression was

utilized as it takes into consideration the skewness and heterogeneity of the cost data and allows us to obtain a more complete picture of the effects of the covariates on the health care cost. Similarly, the cumulative healthcare utilization for each 30-day interval was summed for each patient and zero-inflated negative binomial (ZINB) model was used to predict count of healthcare utilization while adjusting for covariates. ZINB is a type of generalized linear model that may be used when a count-based outcome variable is found to be over dispersed, positively skewed, and zero-inflated (comprised of more zero responses than would be expected given the negative binomial distribution and commonly occurs in health services research with the observation of acute events such as hospitalizations and ER visits) (Moon, 2006).

Statistical significance was set at $P \leq 0.05$. SAS 9.4 (SAS Institute Inc, Cary, North Carolina) was used for all data analyses. This study was approved by National Cancer Institute and the Institutional Review Board at the University of North Carolina at Charlotte.

Results

We identified 16,142 NSCLC patients. Of these patients, 4,652 (28.82%) had T2D before lung cancer diagnosis. Patients differed statistically ($P<0.05$) across several demographic characteristics between NSCLC patients with and without T2D patients (Table 1). The mean age of NSCLC with T2D patients (75 years) was similar to patients without T2D. Majority of patients in the T2D (51 %) were male; however, majority of patients without T2D (59%) group were female. Caucasians accounted for the greatest proportion of lung cancer patients in both diabetic and non-diabetic patients (88% and 93% respectively) followed by African Americans (7% and 4%). The most common comorbid conditions among diabetic and Non-diabetic groups were COPD (53% and 51%), Arrhythmias (33% and 26%) and Peri-Vascular disorder (18% and 11%). The comorbidity status of both groups, measured by the Charlson's Comorbidity Index (CCI), was statistically significant as diabetic patients had a mean score of 5 compared to 3 for non-diabetic patients (Table 1.0).

NSCLC patients with T2D had significantly higher healthcare utilization and subsequent costs in specific healthcare settings and stages, prior to and after adjusting for various covariates (Table 1.1, Table 1.2). Healthcare claims were greater among diabetic NSCLC patients among all settings, compared to NSCLC patients. The most notable difference was in the outpatient setting as for diabetic NSCLC patients compared to NSCLC patients (Stage: I: 0.39 PPPM versus 0.35 PPPM, P<0.05; Stage: II: 0.45 PPPM versus 0.41 PPPM, P <0.12; Stage: IIIA: 0.62 PPPM versus 0.57 PPPM, P <0.34; Stage: IIIB: 0.61 PPPM versus 0.57 PPPM, P <0.05; Stage: IV: 0.75 PPPM versus 0.7 PPPM, P <0.05). Among inpatient visits, healthcare utilization increased by approximately 2.7 times for diabetic NSCLC patients compared to 2.2 times for NSCLC patients from stage I to IV. Overall, there were clear differences between diabetes NSCLC patients and NSCLC patients with higher utilization among diabetic patients (Stage: I: 2 PPPM versus 1.76 PPPM, P <0.05; Stage: II: 2.7 PPPM versus 2.14 PPPM, P <0.34; Stage: IIIA: 3.17 PPPM versus 3.26 PPPM, P<0.29; Stage: IIIB: 3.54 PPPM versus 2.82 PPPM, P <0.05;Stage: IV: 4.48 PPPM versus 4.25 PPPM, P<0.05) (Table 1.2).

Total direct costs in patients with diabetes were significantly higher than NSCLC patients without diabetes, this was observed across all stages (Stage: I: $502.53 PPPM versus $419.98 PPPM, P <0.05; Stage: II: $788.87 PPPM versus $729.95 PPPM, P <0.06;Stage: IIIA: $1101.40 PPPM versus $1070.77 PPPM, P<0.12; Stage: IIIB: $1368.95 PPPM versus $1136.49 PPPM, P <0.05;Stage:IV: $2019.95 PPPM versus $1814.36 PPPM, P<0.05) (Table 1.2).

Physician visits, for stage IIIB and IV patients, had the greatest difference in cost for diabetic NSCLC patients compared to NSCLC patients and was the largest cost category (Stage: I: $251.6 PPPM versus $220.15 PPPM, P<0.29; Stage: II: $394.22 PPPM versus $370.76 PPPM, P<0.17 ; Stage: IIIA: $548.81 PPPM versus $531.98 PPPM, P<0.16;Stage: IIIB: $712.3 PPPM versus $544.58 PPPM, P<0.05; Stage: IV: $959.13 PPPM versus $842.98 PPPM, P<0.05). Emergency room visits increased with stage for NSCLC patients with and without NSCLC and the differences in cost were significant for stage II and IIIB (Stage: I: $14.25 PPPM versus $10.58

PPPM, P <0.15;Stage:II: $17.68 PPPM versus $11.45 PPPM, P <0.05;Stage: IIIA : $18.21 PPPM versus $16.25 PPPM, P<0.23; Stage: IIIB: $22.37 PPPM versus $17.69 PPPM, P <0.05;Stage: IV: $29.26 PPPM versus $25.01 PPPM, P<0.07) (Table 1.2).

Discussion

Our study demonstrated increased healthcare cost and utilization for diabetic non-small cell lung cancer patients in specific healthcare settings. Based on our knowledge, this is the first population-based study to compare utilization of healthcare services between NSCLC with and without T2D. This is distinct from current publications, as it also provides a stratified analysis by cancer stage.

In a longitudinal analysis of healthcare cost and claims, adjusted and unadjusted, there appears to be "U-shaped" curve. This is consistent with the intensity of treatment that is required for initial care. There are spikes in both cost and utilization, more prominent for unadjusted values, which reflect end of life care (Figure 1.0, Figure 1.1). Similar findings were noted when stratified by stage (Figure 1.2, Figure 1.3).

Findings from this study may be impacted by increased comorbidity in this population. The mean number comorbidities, from the Charleston Comorbidity Index, was 5 for diabetic NSCLC patients compared to 3 for NSCLC patients ($p<0.05$). A potential explanation for increase healthcare cost and utilization among diabetic NSCLC patients, is that comorbidity has been demonstrated to intensify healthcare utilization and increase medical cost. Similar trend was observed in a study by Struijs (2006) where an association was observed between the increase of health care utilization and number of comorbidities. Presently, diabetes prevention focuses mainly on micro- and macrovascular comorbidity however, findings from Struijs et al (2006) demonstrate that non-vascular comorbidities are as important utilization drivers as vascular comorbidities, as different comorbid conditions have different effects on health care utilization. Additionally, Shieh and colleagues (2012) attributed comorbid conditions to influence survival of cancer patients and documented elevated risk of mortality for patients. This supported results

from our study that documented greater mortality among diabetic NSCLC patients compared to NSCLC patients (80% versus 77%, respectively, $P<0.05$). While this is statistically significant, it may not be clinically different.

In our findings, indicate that there comorbidities were more prevalent in diabetic NSCLC patients compared to NSCLC patients. Particularly, there was highlighted cardiovascular disease related comorbidities, such as congestive heart failure (CHF). The relationship between diabetes and CHF has been established by the Framingham Study (Kannel, 1974). Diabetes is a cause of congestive heart failure and some form of cardiomyopathy, as a result of either small vessel disease or metabolic disorders. Furthermore, diabetes not only increases the risk of CHF but also accelerates its occurrence (Nichols, 2004). These findings are similar to previously reported literature that indicates. The rate of CHF increase with age and are higher in diabetic patients than in nondiabetic patients (Nichols, 2004). There is a vast amount of need for early recognition and treatment of modifiable risk factors for CHF. The heightened incidence of CHF among the diabetic population emphasizes. While this analysis pertained to adults over the age of 66 years old, this be particularly important for those under the age of 66 as there is greater life expectancy of patients younger than 65 years, and therefore, younger patients may benefit most from modification of intensive risk factors (Nichols, 2004).

In addition to cardiovascular related comorbidity, our results indicate that there were renal failure and anemia were more prevalent among diabetic NSCLC patients. The leading cause of chronic kidney disease (CKD) is diabetes and it is associated with disproportionately higher cardiovascular morbidity and mortality (USRDS, 2007). The most common cause of death for patients with both diabetes and CKD is cardiovascular disease and anemia appears to be associated with increased risk of mortality.

We observed increasing costs across diabetic NSCLC and NSCLC patients with an increase in stage at diagnosis of NSCLC. Conversely, Cipriano et al. found that patients diagnosed with stage I/II NSCLC had a pattern of higher costs in the 6 month period after

diagnosis followed by lower costs in the subsequent post period post diagnosis (Cipriano, 2012). This may be explained by the differences in defining phases of care, as Cipriano defined terminal phase as only the last month of life. However, the relative increased cost of cancer in advanced stage has been consistent with findings in previous literature (Cipriano, 2012; Brown, 2012).

In our study, the proportion of males and females in the diabetic NSCLC group was statistically different than the NSCLC group; prior to studies have proposed various mechanisms to explain the relationship between cancer, diabetes and sex. Males and females differ significantly on various factors, such as hormones, toxicity and efficacy. Authors of a Phase III clinical trial reported differences in clinical outcomes between males and females. In this trial the epidermal growth factor receptor (EGFR), responsible for improved survival, was present in female patients with NSCLC at a higher rate than male NSCLC patients (Pall, 2010). Diabetes management also differs between men and women due to attitudes and beliefs, which drastically impacts being able to live effectively with diabetes (Siddiqui, 2013). While various studies have reported possible explanation of differences between males and females and their interaction with cancer treatment response and comorbidity, the interaction is multifaceted as it is complicated with increasing age of patients as well.

Limitations of this study include issues such as meaningfulness of data available in administrative databases, disease sample size limitations, and generalizability of results given the Medicare sample. Administrative data will generally restrict both the type and scope of research questions that can be addressed. Healthcare claims data has limitations due to data censoring related to the both the amount of available follow up and death, where time of death is unknown. Data collection issues outside of the researcher's control, such as coding errors and diagnosis errors, may introduce non-differential misclassification bias. This has been minimized as diabetes patients were required to have greater than two diagnoses of diabetes in the year, prior to NSCLC. Similarly, the retrospective nature of the study did not permit capturing patient's drug consumption. Findings from this study lacked generalizability, because of limitations of the data

set. Medicare data does not contain data for all populations (eg. healthcare provided by the Veterans Administration) and the study population consisted of elderly NSCLC patients residing in SEER-regions and enrolled in fee for service Medicare. Thus, this lacked generalizability to incident NSCLC patients. Additionally, this study could not obtain information on key risk factors for lung cancer: ethnicity, family history, body mass index, alcohol consumption, smoking consumption, diet, occupational exposure (Molina, 2008). Nonetheless, the methodology and analytic approach helped to minimize many of the potential biases. Future studies should examine if increased duration of metformin use is associated with decreased risk in NSCLC.

Conclusion

In conclusion diabetic NSCLC patients had higher cost, $164.10 more per person per month, and utilization, 0.32 more claims per person per month. The results of our study suggest that the economic burden of diabetic NSCLC is greater than for NSCLC alone. The majority of costs are associated with specific care settings, such as the outpatient setting, emergency room, hospice and outpatient setting. Findings will help inform the body of evidence on diabetes and lung cancer and thus may serve to guide additional research.

This is the first study to quantify healthcare cost and utilization for diabetes patients with NSCLC. This study provides key insights into the economic burden and can be useful to understand the resources that are incurred by the healthcare system as well as payers. Without insights to how comorbid cancer patients utilize the healthcare system it is challenging to initiate discussion around how manage these patients. Findings from this study support the need for subgroup analysis, based on diabetic severity, diabetic medication and cancer stage, of diabetic NSCLC patients to provide additional granularity about healthcare cost and utilization.

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CHAPTER 3 TABLES

Table 3.0 - Patient Characteristics of NSCLC patients with and without T2D

	Diabetic NSCLC Patients (n=4,652)		NSCLC Patients (n=11,490)		
	N	**%**	**N**	**%**	**P Value**
Age at Cancer Diagnosis					0.002
Age 66-69	1008	22%	2818	25%	
Age 70-74	1250	27%	2944	26%	
Age 75-79	1093	23%	2541	22%	
Age 80-84	820	18%	1952	17%	
Age 85+	481	10%	1235	11%	
Age at Cancer Diagnosis					0.055
Mean	75.43		75.23		
SD	6.56		6.83		
Gender					<.0001
Male	2386	51%	4753	41%	
Female	2266	49%	6737	59%	
Race/ Ethnicity					<.0001
White	4096	88%	10687	93%	
Black	341	7%	459	4%	
American Indian/Alaska Native	10	<1%	28	<1%	
Asian or Pacific Islander	196	4%	292	3%	
Stage of Diagnosis					0.059
Stage I	1415	30%	3544	31%	
Stage II	207	4%	452	4%	
Stage IIIA	347	7%	827	7%	
Stage IIIB	748	16%	1690	15%	
Stage IV	1935	42%	4977	43%	
Mortality (% Dead)	3700	80%	8650	75%	<.0001
Geographic Area					<.0001
San Francisco-Oakland	136	3%	342	3%	
Connecticut	253	5%	692	6%	
Metropolitan	392	8%	608	5%	
Hawaii	72	2%	116	1%	
Iowa	257	6%	900	8%	
New	59	1%	210	2%	
Seattle	187	4%	610	5%	
Utah	37	1%	130	1%	
Atlanta	126	3%	330	3%	
San Jose- Monterey	70	2%	226	2%	
Los Angeles	206	4%	547	5%	
Georgia	8	<1%	26	<1%	
Greater California	681	15%	1996	17%	

Kentucky	464	10%	1178	10%	
Louisiana	239	5%	628	5%	
New Jersey	1040	22%	1848	16%	
Georgia	425	9%	1103	10%	
Elixhauser					
Alcohol abuse	75	2%	173	2%	0.618
Blood loss anemia	163	4%	203	2%	<.0001
Arrhythmias	1522	33%	2938	26%	<.0001
Congestive heart failure	411	9%	523	5%	<.0001
Coagulopathy	92	2%	131	1%	<.0001
COPD	2457	53%	5847	51%	0.026
Deficiency anemia	530	11%	665	6%	<.0001
Depression	437	9%	1043	9%	0.528
Drug Abuse	14	<1%	35	<1%	0.969
Fluid and electrolyte disorders	7	<1%	26	<1%	0.334
HIV/AIDS	6	<1%	13	<1%	0.790
Hypertension Uncomplicated	0	0%	1	<1%	0.525
Hypothyroidism	100	2%	187	2%	0.023
Liver disease	402	9%	748	7%	<.0001
Lymphoma	70	2%	131	1%	0.059
Obesity	348	7%	379	3%	<.0001
Other neurological disorders	301	6%	631	5%	0.016
Paralysis	19	<1%	21	<1%	0.009
Peptic ulcer no bleed	103	2%	153	1%	<.0001
Peri-Vascular disorder	818	18%	1255	11%	<.0001
Psychoses	13	<1%	29	<1%	0.760
Pulmonary circulation disorder	122	3%	270	2%	0.308
Renal failure	260	6%	249	2%	<.0001
Rheumatoid arthritis	133	3%	322	3%	0.844
Nonmetastatic tumor	157	3%	340	3%	0.166
Valvular Disease	99	2%	191	2%	0.044
Weight Loss	413	9%	1022	9%	0.973
CCI					<.0001
Mean	5.12		3.02		
Median	4		2		
SD	3.34		2.98		

CCI = Charleston Comorbidity Index; COPD =Chronic Obstructive Pulmonary Disorder; SD= Standard Deviation

Table 3.1 – Healthcare Cost and Claims Stratified by Stage of NSCLC patients with and without T2D (Unadjusted)

				No Diabetes				Diabetes			
Service	NSCLC Stage	Cost Significant	Claim Significant	Person Months	Total Cost	Cost Per Person Per Month	Claim Per Person Per Month	Person Months	Total Cost	Cost Per Person Per Month	Claim Per Person Per Month
Inpatient Admission	I			126,675	$ 1,911,480.11	$ 15.09	0.1082	48,013	$ 490,204.51	$ 10.21	0.1468
Inpatient Admission	II	*		14,611	$ 182,708.12	$ 12.50	0.1300	6,218	$ 312,524.79	$ 50.26	0.1780
Inpatient Admission	IIIA			20,354	$ 920,171.10	$ 45.21	0.1508	7,743	$ 379,843.72	$ 49.05	0.2099
Inpatient Admission	IIIB	*	**	30,185	$ 852,523.78	$ 28.24	0.1935	12,530	$ 624,376.46	$ 49.83	0.2698
Inpatient Admission	IV			58,249	$ 3,636,561.13	$ 62.43	0.2560	20,102	$ 1,210,521.50	$ 60.22	0.3781
Skilled Nursing Facility	I	*		126,675	$ 160,067.89	$ 1.26	0.0153	48,013	$ 27,166.29	$ 0.57	0.0214
Skilled Nursing Facility	II	*	**	14,611	$ 35,246.69	$ 2.41	0.0153	6,218	$ 1,194.19	$ 0.19	0.0272
Skilled Nursing Facility	IIIA			20,354	$ 8,776.21	$ 0.43	0.0203	7,743	$ 3,719.81	$ 0.48	0.0311
Skilled Nursing Facility	IIIB			30,185	$ 28,881.38	$ 0.96	0.0271	12,530	$ 14,483.22	$ 1.16	0.0378
Skilled Nursing Facility	IV		**	58,249	$ 275,898.73	$ 4.74	0.0360	20,102	$ 85,937.52	$ 4.28	0.0534
Physican Visits	I			126,675	$ 55,777,206.28	$ 440.32	2.4782	48,013	$ 25,367,974.67	$ 528.36	2.9811
Physican Visits	II			14,611	$ 10,834,282.69	$ 741.52	3.4273	6,218	$ 4,868,061.87	$ 782.93	4.1747
Physican Visits	IIIA		**	20,354	$ 21,656,371.55	$ 1,063.98	4.2581	7,743	$ 8,499,433.47	$ 1,097.64	4.7130
Physican Visits	IIIB			30,185	$ 32,876,420.96	$ 1,089.17	4.3220	12,530	$ 17,725,906.06	$ 1,414.64	5.3689
Physican Visits	IV	*	**	58,249	$ 98,207,011.32	$ 1,685.98	5.4648	20,102	$ 38,290,469.48	$ 1,904.83	6.7117
Emergency Room Visits	I			126,675	$ 3,217,674.91	$ 25.40	0.0414	48,013	$ 1,359,360.54	$ 28.31	0.0471
Emergency Room Visits	II	*	**	14,611	$ 351,350.52	$ 24.05	0.0415	6,218	$ 220,584.58	$ 35.48	0.0584
Emergency Room Visits	IIIA			20,354	$ 661,852.06	$ 32.52	0.0506	7,743	$ 294,490.22	$ 38.03	0.0647
Emergency Room Visits	IIIB			30,185	$ 1,121,624.30	$ 37.16	0.0559	12,530	$ 556,863.17	$ 44.44	0.0672
Emergency Room Visits	IV			58,249	$ 2,914,786.86	$ 50.04	0.0755	20,102	$ 1,168,285.08	$ 58.12	0.0885

Table 3.1 – Healthcare Cost and Claims Stratified by Stage of NSCLC patients with and without T2D (Unadjusted) (Continued)

				No Diabetes				Diabetes			
Service	NSCLC Stage	Cost Significant	Claim Significant	Person Months	Total Cost	Cost Per Person Per Month	Claim Per Person Per Month	Person Months	Total Cost	Cost Per Person Per Month	Claim Per Person Per Month
Outpatient	I	*	**	126,675	$ 45,197,586.61	$ 356.80	0.7038	48,013	$ 20,091,205.55	$ 418.46	0.7743
Outpatient	II			14,611	$ 8,822,308.70	$ 603.82	0.8690	6,218	$ 3,603,074.06	$ 579.48	0.8952
Outpatient	IIIA			20,354	$ 16,768,824.49	$ 823.85	1.1478	7,743	$ 6,894,366.94	$ 890.35	1.2385
Outpatient	IIIB	*	**	30,185	$ 28,225,822.57	$ 935.10	1.1521	12,530	$ 12,419,708.18	$ 991.17	1.2087
Outpatient	IV	*	**	58,249	$ 82,778,066.85	$ 1,421.10	1.4282	20,102	$ 29,917,916.19	$ 1,488.33	1.5002
Hospice	I			126,675	$ 11,130,997.89	$ 87.87	0.0246	48,013	$ 4,389,281.53	$ 91.42	0.0255
Hospice	II	*	**	14,611	$ 1,431,520.89	$ 97.98	0.0287	6,218	$ 950,121.79	$ 152.81	0.0426
Hospice	IIIA			20,354	$ 4,119,383.67	$ 202.38	0.0582	7,743	$ 1,459,302.31	$ 188.46	0.0548
Hospice	IIIB	*	**	30,185	$ 9,416,366.42	$ 311.96	0.0907	12,530	$ 3,176,802.03	$ 253.53	0.0795
Hospice	IV			58,249	$ 25,748,314.25	$ 442.04	0.1356	20,102	$ 9,709,893.81	$ 483.04	0.1469
Pharmacy	I			126,675	$ 327,133.45	$ 2.58	0.0271	48,013	$ 121,279.53	$ 2.53	0.0285
Pharmacy	II			14,611	$ 52,564.03	$ 3.60	0.0299	6,218	$ 13,780.26	$ 2.22	0.0330
Pharmacy	IIIA			20,354	$ 102,509.51	$ 5.04	0.0396	7,743	$ 50,520.94	$ 6.52	0.0433
Pharmacy	IIIB			30,185	$ 262,118.40	$ 8.68	0.0531	12,530	$ 105,588.93	$ 8.43	0.0571
Pharmacy	IV			58,249	$ 929,819.44	$ 15.96	0.0808	20,102	$ 320,936.30	$ 15.97	0.0913
Total	I	*	**	126,675	$ 114,504,472.23	$ 903.92	3.3572	48,013	$ 50,487,112.08	$ 1,051.54	3.9776
Total	II			14,611	$ 21,358,631.12	$ 1,461.83	4.50	6,218	$ 9,748,756.96	$ 1,567.90	5.3507
Total	IIIA			20,354	$ 43,576,036.53	$ 2,140.89	5.67	7,743	$ 17,287,187.19	$ 2,232.51	6.2905
Total	IIIB	*	**	30,185	$ 71,662,133.51	$ 2,374.11	5.84	12,530	$ 34,066,864.88	$ 2,718.74	7.0217
Total	IV	*	**	58,249	$ 211,575,671.72	$ 3,632.24	7.40	20,102	$ 79,535,674.80	$ 3,956.66	8.8816

*P<0.05

Table 3.2 – Healthcare Cost and Claims Stratified by Stage of NSCLC patients with and without T2D (Adjusted)

		Significant		No Diabetes				Diabetes			
Service	NSCLC Stage	Cost	Claim	Person Months	Total Cost	Cost Per Person Per Month	Claim Per Person Per Month	Person Months	Total Cost	Cost Per Person Per Month	Claim Per Person Per Month
Inpatient Admission	I			126,675	$ 955,740.06	$ 7.54	0.0618	48,013	$ 246,830.06	$ 5.14	0.0741
Inpatient Admission	II	*		14,611	$ 91,354.06	$ 6.25	0.0644	6,218	$ 153,650.34	$ 24.71	0.0899
Inpatient Admission	IIIA			20,354	$ 460,085.55	$ 22.60	0.0715	7,743	$ 191,260.69	$ 24.70	0.1060
Inpatient Admission	IIIB	*	**	30,185	$ 405,963.70	$ 13.45	0.0977	12,530	$ 314,388.96	$ 25.09	0.1363
Inpatient Admission	IV			58,249	$ 1,818,280.57	$ 31.22	0.1362	20,102	$ 609,527.44	$ 30.32	0.1909
Skilled Nursing Facility	I	*	**	126,675	$ 76,222.80	$ 0.60	0.0077	48,013	$ 12,936.33	$ 0.27	0.0108
Skilled Nursing Facility	II	*	**	14,611	$ 16,784.14	$ 1.15	0.0073	6,218	$ 568.66	$ 0.09	0.0137
Skilled Nursing Facility	IIIA			20,354	$ 3,815.74	$ 0.19	0.0101	7,743	$ 1,873.02	$ 0.24	0.0157
Skilled Nursing Facility	IIIB			30,185	$ 14,440.69	$ 0.48	0.0137	12,530	$ 7,292.66	$ 0.58	0.0191
Skilled Nursing Facility	IV		**	58,249	$ 137,949.37	$ 2.37	0.0172	20,102	$ 43,271.66	$ 2.15	0.0270
Physican Visits	I			126,675	$ 27,888,603.14	$ 220.16	1.3182	48,013	$ 12,079,987.94	$ 251.60	1.5056
Physican Visits	II			14,611	$ 5,417,141.35	$ 370.76	1.6320	6,218	$ 2,451,189.26	$ 394.23	2.1084
Physican Visits	IIIA		**	20,354	$ 10,828,185.78	$ 531.99	2.5498	7,743	$ 4,249,716.74	$ 548.82	2.3803
Physican Visits	IIIB			30,185	$ 16,438,210.48	$ 544.59	2.0581	12,530	$ 8,925,431.05	$ 712.30	2.7116
Physican Visits	IV	*	**	58,249	$ 49,103,505.66	$ 842.99	3.2920	20,102	$ 19,280,196.11	$ 959.13	3.3898
Emergency Room Visits	I			126,675	$ 1,340,697.88	$ 10.58	0.0222	48,013	$ 684,471.57	$ 14.26	0.0238
Emergency Room Visits	II	*	**	14,611	$ 167,309.77	$ 11.45	0.0205	6,218	$ 109,932.59	$ 17.68	0.0295
Emergency Room Visits	IIIA			20,354	$ 330,926.03	$ 16.26	0.0254	7,743	$ 141,062.75	$ 18.22	0.0327
Emergency Room Visits	IIIB	*		30,185	$ 534,106.81	$ 17.69	0.0280	12,530	$ 280,394.35	$ 22.38	0.0339
Emergency Room Visits	IV			58,249	$ 1,457,393.43	$ 25.02	0.0429	20,102	$ 588,260.36	$ 29.26	0.0447

Table 3.2 – Healthcare Cost and Claims Stratified by Stage of NSCLC patients with and without T2D (Adjusted) (Continued)

		Significant		No Diabetes				Diabetes			
Service	NSCLC Stage	Cost	Claim	Person Months	Total Cost	Cost Per Person Per Month	Claim Per Person Per Month	Person Months	Total Cost	Cost Per Person Per Month	Claim Per Person Per Month
Outpatient	I	*	**	126,675	$ 18,832,327.75	$ 148.67	0.3554	48,013	$ 9,634,221.52	$ 200.66	0.3910
Outpatient	II			14,611	$ 4,411,154.35	$ 301.91	0.4138	6,218	$ 1,814,236.69	$ 291.78	0.4521
Outpatient	IIIA			20,354	$ 8,384,412.25	$ 411.93	0.5797	7,743	$ 3,287,728.63	$ 424.58	0.6255
Outpatient	IIIB	*	**	30,185	$ 12,829,919.35	$ 425.05	0.5798	12,530	$ 6,253,629.50	$ 499.08	0.6104
Outpatient	IV	*	**	58,249	$ 39,418,127.07	$ 676.71	0.7035	20,102	$ 15,064,408.96	$ 749.41	0.7577
Hospice	I			126,675	$ 5,300,475.19	$ 41.84	0.0124	48,013	$ 2,093,124.24	$ 43.60	0.0129
Hospice	II	*	**	14,611	$ 708,673.71	$ 48.50	0.0145	6,218	$ 478,409.76	$ 76.94	0.0215
Hospice	IIIA			20,354	$ 2,059,691.84	$ 101.19	0.0348	7,743	$ 772,608.17	$ 99.78	0.0277
Hospice	IIIB	*	**	30,185	$ 4,483,984.01	$ 148.55	0.0456	12,530	$ 1,599,598.20	$ 127.66	0.0401
Hospice	IV			58,249	$ 14,713,322.43	$ 252.59	0.0682	20,102	$ 5,427,553.83	$ 270.00	0.0742
Pharmacy	I			126,675	$ 148,697.02	$ 1.17	0.0130	48,013	$ 61,067.24	$ 1.27	0.0144
Pharmacy	II			14,611	$ 20,216.93	$ 1.38	0.0151	6,218	$ 6,938.70	$ 1.12	0.0167
Pharmacy	IIIA			20,354	$ 58,576.86	$ 2.88	0.0200	7,743	$ 25,438.54	$ 3.29	0.0218
Pharmacy	IIIB			30,185	$ 132,383.03	$ 4.39	0.0268	12,530	$ 53,166.63	$ 4.24	0.0288
Pharmacy	IV			58,249	$ 494,584.81	$ 8.49	0.0408	20,102	$ 179,534.74	$ 8.93	0.0461
Total	I	*	**	126,675	$ 53,202,065.96	$ 419.99	1.7686	48,013	$ 24,128,167.32	$ 502.54	2.0089
Total	II			14,611	$ 10,665,324.54	$ 729.96	2.1472	6,218	$ 4,904,993.41	$ 788.87	2.7024
Total	IIIA			20,354	$ 21,794,768.01	$ 1,070.77	3.2658	7,743	$ 8,528,625.78	$ 1,101.41	3.1770
Total	IIIB	*	**	30,185	$ 34,304,901.26	$ 1,136.49	2.8217	12,530	$ 17,153,506.99	$ 1,368.95	3.5463
Total	IV	*	**	58,249	$ 105,685,769.90	$ 1,814.37	4.2578	20,102	$ 40,604,492.75	$ 2,019.95	4.4856

*P<0.05

CHAPTER 3 FIGURES

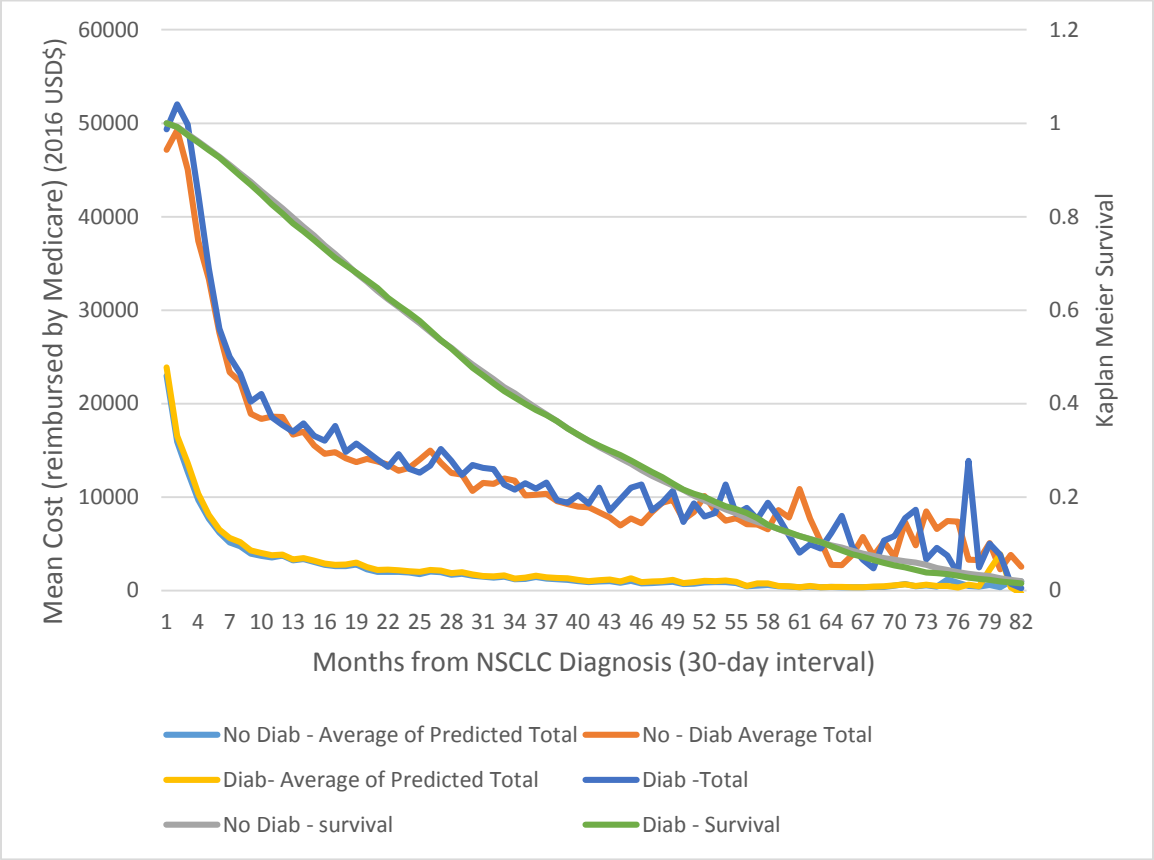

Figure 3.0 – Healthcare Cost Adjusted & Unadjusted

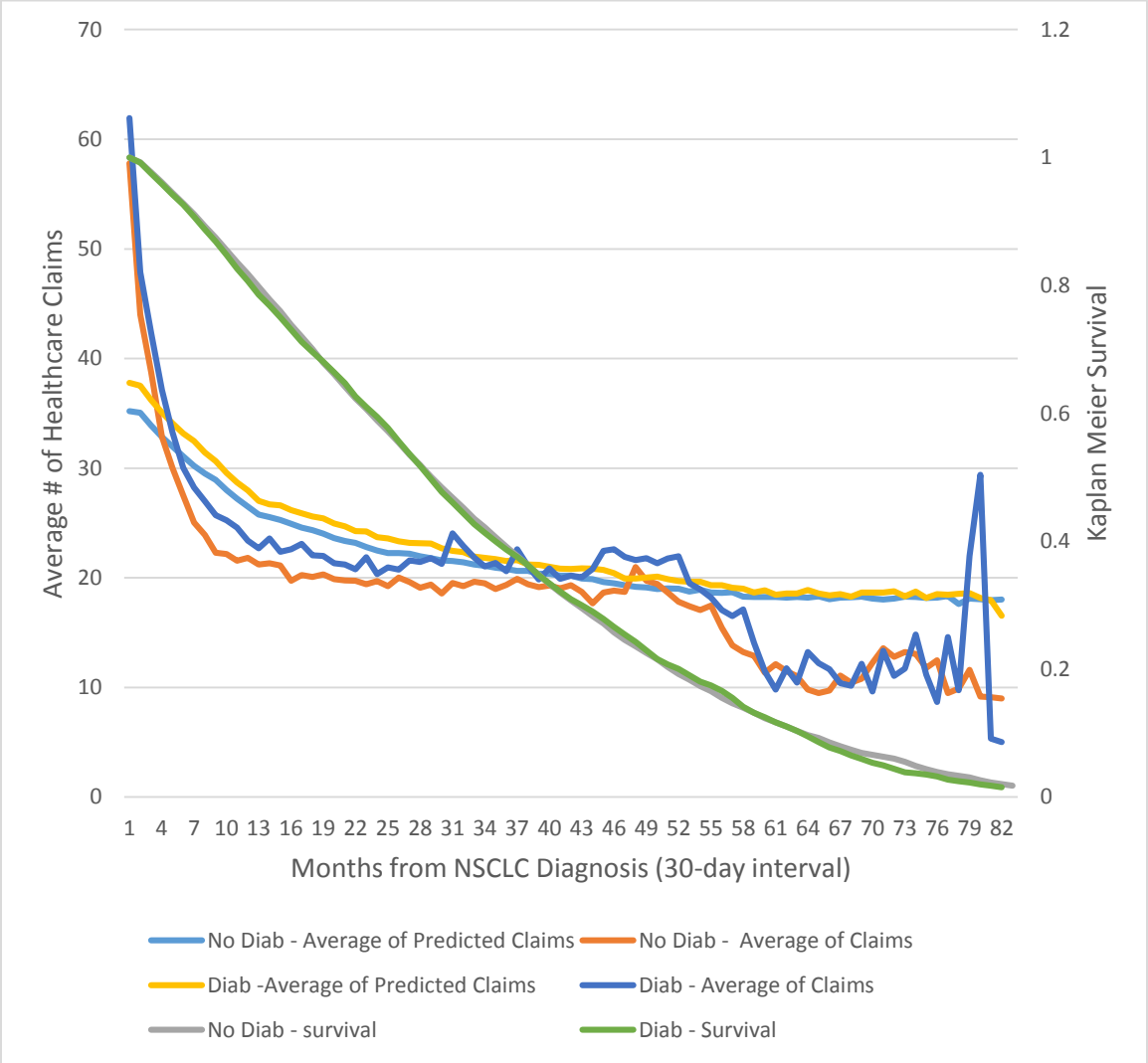

Figure 3.1 - Healthcare Claims Adjusted & Unadjusted

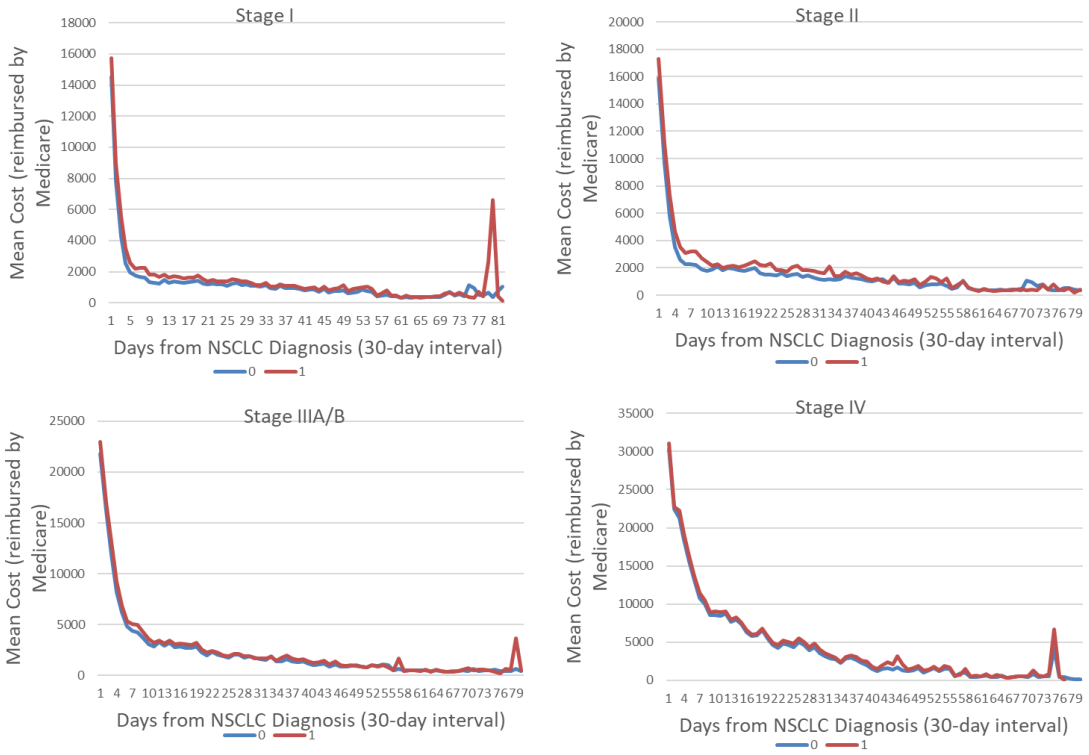

Figure 3.2 – Healthcare Cost Adjusted Stratified by Stage

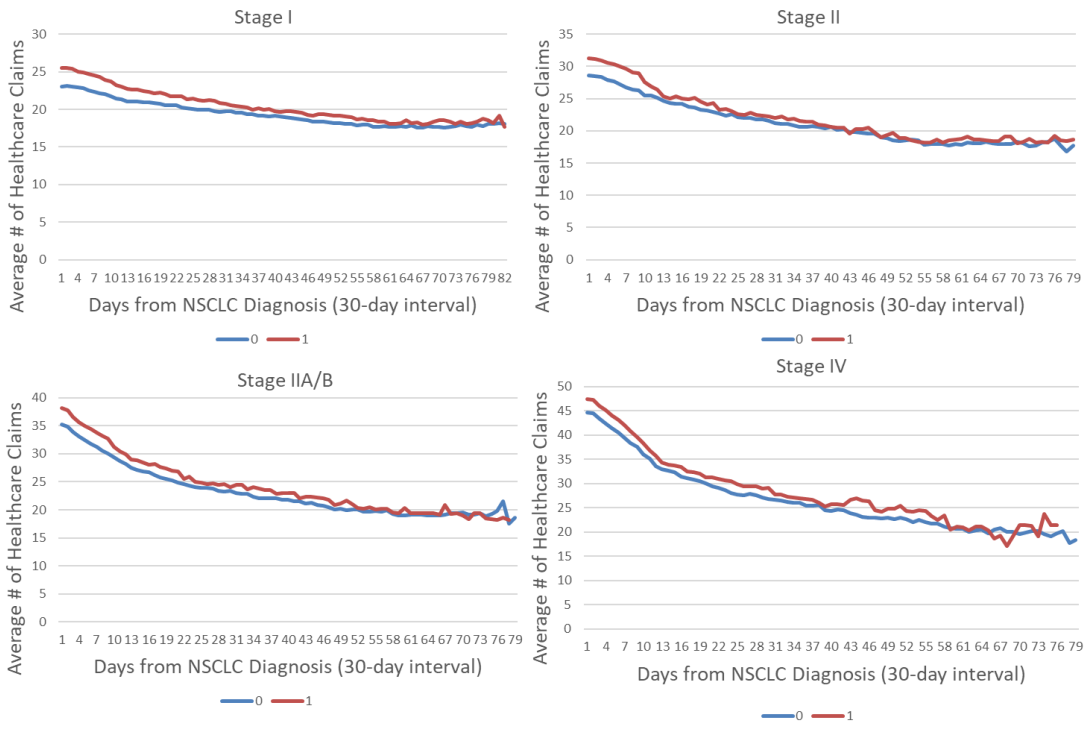

Figure 3.3 - Healthcare Claims Adjusted Stratified by Stage

Chapter 4: The association between incident metformin exposure and Non-Small Cell Lung Cancer diagnosis among diabetic patients

Introduction

Lung cancer is the principal cause of cancer mortality worldwide, accounting for approximately 1.3 million deaths each year (Ries, 2005). There is increasing evidence linking metformin use to decreased cancer risk and improved outcomes (Marchesini, 2005; Nathan, 2009; Hundal, 2000). Metformin is a part of the biguanide class of oral hypoglycaemic agents and is a regularly prescribed medication for various conditions including diabetes, polycystic ovary syndrome (Nestler, 2008) and non-alcoholic fatty liver disease (Marchesini, 2005). For T2D, it is the first-line drug of choice among patients with normal kidney function (Nathan, 2009).

Metformin may influence cancer cells through indirect (insulin-related) effects, or by directly influencing cancer cell proliferation and apoptosis (Hadad, 2008), and may influence the risk and development of cancer and its prognosis.

In a meta-analysis conducted by Wan and colleagues (2016) a comprehensive analysis produced 17 individual studies from 10 publications. Findings from the results revealed a significant association of metformin use with a better survival of lung cancer patients with diabetes (for disease free survival (DFS): HR = 0.65, 95%CI = 0.52-0.83; for OS: HR = 0.78, 95%CI = 0.64-0.93). Stratification of findings are consistent in non-small cell lung cancer (for DFS: HR = 0.70, 95%CI = 0.51-0.96; for overall survival(OS): HR = 0.75, 95%CI = 0.58- 0.97) and a reduction in the risk of cancer-related mortality in patients receiving chemotherapy(for DFS: HR = 0.71, 95%CI = 0.64-0.83; for OS: HR= 0.58, 95%CI = 0.47-0.71). Similarly, Zhang et al. (2014) summarized lung cancer and diabetes studies from 2009–2013 and explored the rationale of heterogeneity. Metformin therapy was associated with significantly lower risks of lung cancer (4 studies; pooled relative risk = 0.71, 95% confidence interval (CI): 0.55, 0.95; P = 0.02). However, authors documented that a major source of heterogeneity was adjustment of smoking status and cancer site. Conversely, in a Meta-analysis of cohort studies by Zhu et al.

(2016) was utilized to derive an accurate estimate of the role of T2D in lung cancer. Authors employed Medline and Embase for eligible articles to October 2015. Findings from this study indicate a significant correlation between T2D state with poor survival in lung cancer patients, especially in the subgroup of surgically treated NSCLC patients (Zhu, 2016). While various of studies have described the association between metformin and survival, limited number of studies have assessed the relationship between incident metformin and anti-diabetic drug medication and time to NSCLC diagnosis.

Therefore, given the limited studies that have assessed how metformin may impact patients' NSCLC diagnosis, our objective is to investigate the time from incident antidiabetic drug medication to NSCLC diagnosis among metformin impact compared to other antidiabetic drug medication users with co-morbid NSCLC and T2D.

Methods

Data Source

A retrospective database study of linked cancer registry data (SEER) and Medicare claims was conducted. The SEER – Medicare linked databases provided a temporal view of patients with T2D and NSCLC (2007 - 2013). The SEER program collects data on incident cancer diagnosis within a defined geographic area. The program originated in 1973, now includes registries that cover about 26 percent of the U.S. population (Warne, 2002). Data including patient's age, race, sex, and marital status are included in addition to details about cancer diagnosis including the month and year of diagnosis, behavior, the site, and stage based on a classification that can vary by cancer site as well as year of diagnosis (Warne, 2002).

Study Population

Patients were included in the study if they were diagnosed with NSCLC between January 01, 2008 and December 31, 2013, at least 66 years old, continuous enrollment in Medicare A and B in the 12 months prior to diagnosis. Patients were excluded if their date of death recorded was

prior to or in the same month of diagnosis and if they were enrolled in an HMO at anytime during the 12 months prior to diagnosis, as complete claims for these patients were unavailable.

NSCLC diagnosis was based on the International Classification of Disease for Oncology (3rd edition, ICD-O-3) histology codes in the SEER Medicare data. Tumor stage was classified according to the 6th edition of the American Joint Commission on Cancer. Diagnosis of preexisting T2D in NSCLC patients was identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) 250.xx prior to cancer diagnosis utilizing Medicare claims files.

For both cases and controls incident medication was defined as patients that did have a claim for an anti-diabetic drug medication 90-days preceding the first observed claim of an anti-diabetic drug. Cases were defined as incident metformin user and may be combination therapy users, after initial metformin utilization. Controls were defined as incident users of other anti-diabetic drug medications which only included Dipipeptidyl peptidase 4 (DPP-4), Sulfonylurea and Thiazolidinedione. The date of cohort entry was defined as the date of incident antidiabetic drug medication. Cases and controls were matched on their propensity score at a 3:1 ratio, given excess number of metformin users (Parsons, 2004).

Statistical Analysis

Descriptive statistics were utilized to summarize demographic and clinical characteristics by metformin and other anti-diabetic users. Differences between groups were assessed using chi-square tests for categorical and t tests for continuous variables, prior to matching. After matching both groups, Standardized differences were calculated, before and after matching, to assess the balance between the metformin and other antidiabetic drug medication groups, with values greater than 0.2 indicating imbalance. Time to incident NSCLC was measured from date of incident metformin or other ADM to NSCLC diagnosis date. In the overall survival analysis, comparisons were made between NSCLC patients with diabetes and for all stages of cancer. Kaplan Meier and log rank tests were used to examine time to NSCLC for cases and controls.

Multivariable survival analysis was completed by Cox-proportional hazards models. Cox-proportional hazards models were used to assess progression to NSCLC adjusted for baseline demographics (age, sex, and race/ethnicity). The effects of cumulative duration of exposure to antidiabetic medication was assessed by using a Cox-proportional hazards model. To avoid survival bias, those who take metformin longer are predetermined to survive longer, so cumulative drug exposure was modeled as a time-dependent covariate.

Statistical significance was set at $P \leq 0.05$. SAS 9.4 (SAS Institute Inc, Cary, North Carolina) was used for all data analyses. This study was approved by National Cancer Institute and the Institutional Review Board at the University of North Carolina at Charlotte.

Results

We identified 4, 652 patients aged older than 66 years with T2D prior to diagnosis of NSCLC. Of these T2D NSCLC patients 692 were incident metformin users and 161 were incident other anti-diabetic drug medication users. Prior to matching metformin patients and other anti-diabetic drug medication users were similar in age (76.5 years versus 74.9 years, respectively). There were not any statistical differences in gender, race, stage, mortality or geographic variation. Differences in comorbidities between the metformin and other ADM users, included significantly greater hypothyroidism, per-vascular disorder, renal failure, congestive heart failure and arrhythmias ($p<0.005$) (Table 21). Patients included in the other ADM group had a significantly higher CCI score 6.12 (3.28) compared to the metformin group ($p<0.001$). After matching, 400 patients were assigned as cases (n = 300) and controls (n = 100). Differences in comorbidities were less apparent (using the standardized mean difference) (Table 2.2).

The overall median survival was longer in the Metformin NSCLC group (685 days) compared to the other ADM NSCLC group (523 days; log rank $p<0.004$) (Figure 2.0). However, after accounting for various covariates, in the multivariate cox proportional hazard model, there were no statistically significant associations between incident metformin and time to NSCLC

(Table 2.2). Similar findings were observed in a sensitivity analysis was conducted which included the total amount of metformin and/or antidiabetic drug medication (Table 2.3).

Discussion

Our results indicate that diabetic patients over the age of 66 years old on metformin did consistently have a greater time to NSCLC diagnosis than, diabetic patients over the age of 66 years old on other antidiabetic drug medication.

Prior studies have reported that metformin has a survival benefit in various malignancies, such as prostate, breast, and colorectal cancer; however, there are limited data is available regarding the potential effectiveness of metformin among patients with lung cancer. In a study by Libby et al (2009), an observational cohort study, using record-linkage databases and based in Tayside, Scotland, U.K., patients with type 2 diabetes who were new users of metformin were identified. Results from this study indicate that the unadjusted hazard ratio (95% CI) for cancer was 0.46 (0.40–0.53). Upon adjusting for various factors include, gender, age, BMI, A1C, smoking, and other drug use, a significantly reduced risk of cancer associated with metformin still remained, 0.63 (0.53–0.75). Lin et al (2014) had similar findings when comparing overall survival of patients with diabetes with stage IV NSCLC taking metformin versus those not on metformin. Results indicate that, after controlling for factors like, sociodemographic, diabetes severity, cancer treatment and other diabetes medications, metformin use was associated with a statistically significant improvement in survival (hazard ratio, 0.80; 95% confidence interval, 0.71–0.89).

Several mechanisms have been proposed to assess the association between metformin and NSCLC, specifically metformin. Metformin may influence cancer cells through indirect (insulin-related) effects, or by directly influencing cancer cell proliferation and apoptosis (Hadad, 2008). Metformin's suggested mechanism of action in preventing cancer is via the AMPK pathway (Hadad, 2008). AMPK is a cellular fuel sensor pathway sensitive to heightened AMP/ATP ratio (Kahn, 2005). Furthermore, AMPK activation within cancer cells has been

shown to inhibit the mTORC1 pathway and S6K1 phosphorylation (via the TSC complex) implicated in protein synthesis (Kahn, 2005). Metformin also activates the AMPK pathway in the liver causing decreased gluconeogenesis, which leads to a decrease in insulin levels (Kahn, 2005). This indirectly leads to decreased action of insulin on cancer cells, which inhibits the mTOR pathway. Ergo, metformin has two actions on this axis (reducing stimulation of the insulin receptor and reducing signaling through the mTOR pathway) thereby reducing the end effects of mTOR signaling (Pollak, 2010).

There was limited literature that discussed the association between incident metformin users and incident cancer. However, one study, (Libby, 2009), assessed the risk of incident cancer for incident metformin users. Authors utilized the record-linkage databases and based in the United Kingdom and cancer types included, breast, lung and bowel cancer. Similar to findings from our study, authors documented a significantly greater median time to NSCLC for metformin users compared to non-metformin users (3.5 and 2.6 years, respectively ($P < 0.001$).

Limitations of this study include issues such as meaningfulness of data available in administrative databases, disease sample size limitations, and generalizability of results given the Medicare sample. Administrative data will generally restrict both the type and scope of research questions that can be addressed. Healthcare claims data has limitations due to data censoring related to the both the amount of available follow up and death, where time of death is unknown. Data collection issues outside of the researcher's control, such as coding errors and diagnosis errors, may introduce non-differential misclassification bias. This has been minimized as diabetes patients were required to have greater than two diagnoses of diabetes in the year, prior to NSCLC. Similarly, the retrospective nature of the study did not permit capturing patient's drug consumption. Findings from this study lacked generalizability, because of limitations of the data set. Medicare data does not contain data for all populations (eg. healthcare provided by the Veterans Administration) and the study population consisted of elderly NSCLC patients residing in SEER-regions and enrolled in fee for service Medicare. Thus, this lacked generalizability to

incident NSCLC patients. Additionally, this study could not obtain information on key risk factors for lung cancer: ethnicity, family history, body mass index, alcohol consumption, smoking consumption, diet, occupational exposure (Molina, 2008). Given the nature of our study population based observational study treatment was not randomly assigned and differences between individuals treated with different drugs or for differing lengths of time may be related to the outcomes independent of the effects of Metformin. Finally, metformin and diabetes are tied to the same measure, therefore, we cannot measure the effect of metformin on NSCLC independently. Nonetheless, the methodology and analytic approach helped to minimize many of the potential biases. Future studies should examine if increased duration of metformin use is associated with decreased risk in NSCLC.

Conclusion

In summary, this data suggests that among patients with diabetes metformin use was associated with increased time to NSCLC diagnosis, however, with the introduction of covariates, the difference in survival is not statistically significant. Our results contribute additional evidence validating the potential anticancer effects of metformin. This study has produced sufficient epidemiological evidence that metformin reduces the risk of cancer to make further investigation a high priority. Future studies with more recent clinical data in conjunction with cancer therapies can help determine if metformin is an effective treatment for lung cancer patients.

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CHAPTER 4 TABLES

Table 4.0 - Patient Characteristics of T2D NSCLC Patients on Metformin versus Other Antidiabetic Drug Medication (Prior to Matching)

	Metformin (Mono or Combo) (n=692)		**Other ADM Users (excluding insulin) (n=161)**		
	N	**%**	**N**	**%**	**P-Value**
Age at Cancer Diagnosis					0.021
Age 65-69	145	21%	20	12%	
Age 70-74	222	32%	51	32%	
Age 75-79	161	23%	39	24%	
Age 80-84	114	16%	29	18%	
Age 85+	50	7%	22	14%	
Age at Cancer Diagnosis					0.329
Mean	76.52		74.89		
SD	6.37		6.05		
Gender					0.530
Male	350	51%	77	48%	
Female	342	49%	84	52%	
Race/ Ethnicity					0.217
White	625	90%	138	86%	
Black	36	5%	14	9%	
American Indian/Alaska Native	3	<1%	0	<1%	
Asian or Pacific Islander	28	4%	9	6%	
Stage of Diagnosis					0.895
Stage I	225	33%	49	30%	
Stage II	42	6%	10	6%	
Stage IIIA	45	7%	14	9%	
Stage IIIB	98	14%	23	14%	
Stage IV	282	41%	65	40%	
Mortality (% Dead)	533	77%	130	81%	0.307
Geographic Area					0.665
San Francisco-Oakland	13	2%	7	4%	
Connecticut	33	5%	8	5%	
Metropolitan	49	7%	7	4%	
Hawaii	8	1%	3	2%	
Iowa	37	5%	11	7%	
New	8	1%	1	1%	
Seattle	33	5%	6	4%	
Utah	7	1%	1	1%	
Atlanta	15	2%	4	2%	
Alaska	0	0%		0%	

San Jose- Monterey	13	2%	2	1%	
Los Angeles	32	5%	8	5%	
Georgia	1	<1%	0	<1%	
Greater California	105	15%	20	12%	
Kentucky	86	12%	17	11%	
Louisiana	43	6%	8	5%	
New Jersey	139	20%	45	28%	
Georgia	70	10%	13	8%	
Elixhauser					
Alcohol abuse	10	1%	3	2%	0.696
Blood loss anemia	21	3%	2	1%	0.206
Arrhythmias	201	29%	61	38%	0.029
Congestive heart failure	48	7%	21	13%	0.011
Coagulopathy	12	2%	2	1%	0.658
COPD	378	55%	93	58%	0.471
Deficiency anemia	68	10%	21	13%	0.229
Depression	66	10%	19	12%	0.388
Drug Abuse	3	<1%	1	1%	0.754
HIV/AIDS	1	0%	0	0%	0.629
Hypothyroidism	5	1%	9	6%	<.0001
Liver disease	50	7%	16	10%	0.246
Lymphoma	12	2%	4	2%	0.527
Obesity	63	9%	13	8%	0.680
Other neurological disorders	46	7%	12	7%	0.714
Paralysis	1	<1%	0	0%	0.629
Peptic ulcer no bleed	15	2%	7	4%	0.116
Peri-Vascular disorder	92	13%	42	26%	<.0001
Psychoses	4	1%	1	1%	0.949
Pulmonary circulation disorder	19	3%	7	4%	0.287
Renal failure	16	2%	24	15%	<.0001
Rheumatoid arthritis	18	3%	6	4%	0.437
Nonmetastatic tumor	19	3%	5	3%	0.804
Valvular Disease	16	2%	6	4%	0.308
Weight Loss	66	10%	18	11%	0.529
CCI					<.0001
Mean	4.83		6.17		
Median	4.00		6.00		
SD	3.20		3.28		

CCI = Charleston Comorbidity Index; COPD =Chronic Obstructive Pulmonary Disorder; SD= Standard Deviation

Table 4.1 – Patient Characteristics of T2D NSCLC Patients on Metformin versus Other Antidiabetic Drug Medication (Post Matching)

	Metformin (Mono or Combo) (n=300)		**Other ADM Users (excluding insulin) (n=100)**		
	N	**%**	**N**	**%**	**Standardized Difference***
Age at Cancer Diagnosis					0.110
Age 66-69	45	15%	18	18%	
Age 70-74	112	37%	33	33%	
Age 75-79	78	26%	26	26%	
Age 80-84	38	13%	14	14%	
Age 85+	27	9%	9	9%	
Age at Cancer Diagnosis					0.002
Mean	75.22		75.19		
SD	5.89		6.04		
Gender					0.041
Male	161	54%	44	44%	
Female	139	46%	56	56%	
Race/ Ethnicity					0.131
White	45	15%	18	18%	
Black	112	37%	33	33%	
American Indian/Alaska Native	78	26%	26	26%	
Asian or Pacific Islander	38	13%	14	14%	
Other unspecified	27	9%	9	9%	
Stage of Diagnosis					0.127
Stage I	102	34%	34	34%	
Stage II	15	5%	7	7%	
Stage IIIA	23	8%	9	9%	
Stage IIIB	44	15%	16	16%	
Stage IV	116	39%	34	34%	
Mortality (% Dead)	235	78%	77	77%	0.032
Geographic Area					0.401
San Francisco-Oakland	6	2%	4	4%	
Connecticut	14	5%	4	4%	
Metropolitan	24	8%	4	4%	
Hawaii	1	0%	2	2%	
Iowa	15	5%	8	8%	
New	2	1%	1	1%	
Seattle	16	5%	5	5%	
Atlanta	7	2%	2	2%	
Alaska	0	0%	2	2%	
San Jose- Monterey	7	2%	0	0%	
Los Angeles	17	6%	5	5%	

Georgia	1	<1%	0	0%	
Greater California	48	16%	11	11%	
Kentucky	40	13%	14	14%	
Louisiana	19	6%	4	4%	
New Jersey	53	18%	26	26%	
Georgia	30	10%	8	8%	
Elixhauser					
Alcohol abuse	4	1%	3	3%	0.048
Blood loss anemia	11	4%	1	1%	0.130
Arrhythmias	98	33%	36	36%	0.107
Congestive heart failure	25	8%	10	10%	0.058
Coagulopathy	3	1%	1	1%	0.095
COPD	179	60%	59	59%	0.071
Deficiency anemia	35	12%	10	10%	0.127
Depression	29	10%	12	12%	0.066
Drug Abuse	0	0%	1	1%	0.003
HIV/AIDS	1	<1%	0	0%	0.150
Hypertension Uncomplicated	0	0%	0	0%	0.098
Hypothyroidism	1	0%	1	1%	0.076
Liver disease	24	8%	7	7%	0.054
Lymphoma	6	2%	2	2%	0.088
Obesity	26	9%	7	7%	0.165
Other neurological disorders	22	7%	6	6%	0.088
Peptic ulcer no bleed	11	4%	3	3%	0.140
Peri-Vascular disorder	41	14%	19	19%	0.181
Psychoses	3	1%	0	0%	0.099
Pulmonary circulation disorder	10	3%	5	5%	0.123
Renal failure	3	1%	0	0%	0.198
Rheumatoid arthritis	9	3%	3	3%	0.027
Nonmetastatic tumor	11	4%	2	2%	0.054
Valvular Disease	11	4%	5	5%	0.179
Weight Loss	30	10%	7	7%	0.024
CCI					
Mean	5.89		5.17		0.231
Median	5.00		5.00		
SD	3.27		2.90		

CCI = Charleston Comorbidity Index; COPD =Chronic Obstructive Pulmonary Disorder; SD= Standard Deviation

* Standardized difference = difference in means or proportions divided by standard error; imbalance defined as value greater than 0.20 (small effect size).

Table 4.2 – Cox Proportional Hazard Model for T2D NSCLC Patients on Metformin versus Other Antidiabetic Drug Medication*

		Confidence Interval	
Stage	**Hazard Ratio**	**Lower**	**Higher**
Stage I	0.689	0.452	1.05
Stage II	0.197	0.038	1.029
Stage IIIA	0.139	0.014	1.329
Stage IIIB	0.908	0.459	1.795
Stage IV	0.694	0.47	1.026
All	0.828	0.651	1.055

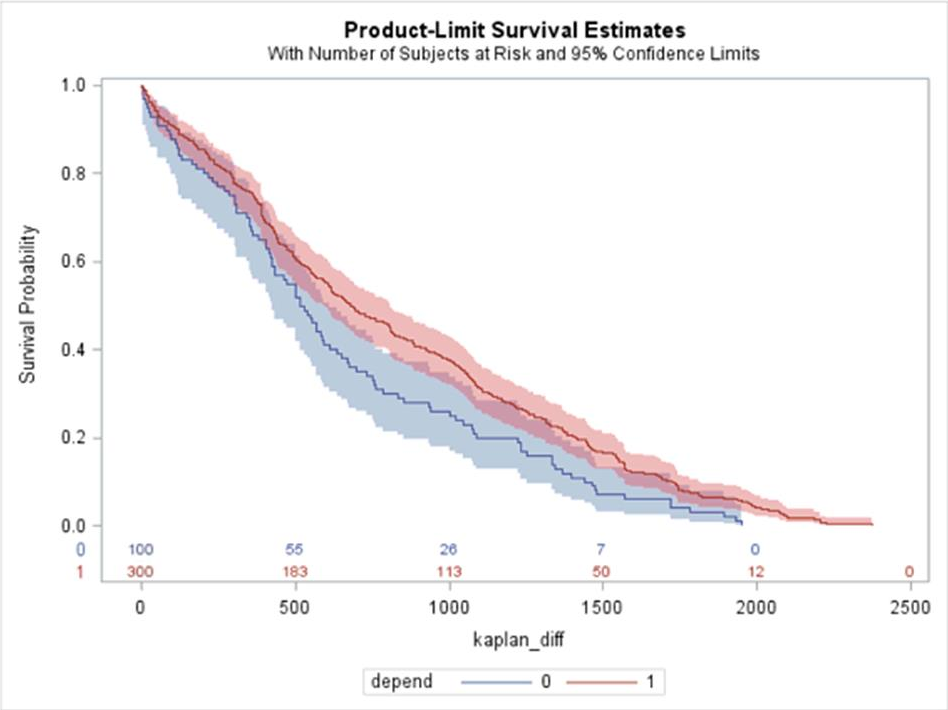
Note: Other Antidiabetic Non Small Cell Lung Cancer Patients = Reference Group
* Adjusted for Covariates

Table 4.3 – Cox Proportional Hazard Model for T2D NSCLC Patients on Metformin versus Other Antidiabetic Drug Medication (Sensitivity Analysis)

		Confidence Interval	
Stage	**Hazard Ratio**	**Lower**	**Higher**
Stage I	0.69	0.45	1.058
Stage II	0.34	0.043	2.677
Stage IIIA	0.92	0.303	2.798
Stage IIIB	0.93	0.474	1.825
Stage IV	1.06	0.669	1.679
All	0.774	0.605	0.991

Note: Other Antidiabetic Non Small Cell Lung Cancer Patients = Reference Group
* Adjusted for Covariates

CHAPTER 4 FIGURES



Group	Mean Days	Median Days
Metformin (1)	828.06	685.50
Other ADM (0)	659.20	523.00

Log Rank = 0.0041

Figure 4.0 - Kaplan Meier Survival Analysis of Diabetic NSCLC Patients on Metformin versus Patients on Other Antidiabetic Drug Medication

Chapter 5: The association between metformin exposure and survival among diabetic patients with Non-Small Cell Lung Cancer

Introduction

Lung cancer is the second most commonly diagnosed cancer in men and women. An estimated 224,390 new cases of lung cancer are expected in 2016, accounting for about 14% of all cancer diagnoses (Siegel, 2015). The incidence rate has been diminishing since the mid-1980s in men, but only since the mid-2000s in women (Tarver, 2012). From 2007 to 2011, lung cancer incidence rates declined by 3.0% per year in men and by 2.2% per year in women (Siegel, 2015). It is estimated that 221,200 new cases of lung cancer are expected in 2015, accounting for about 13% of all cancer diagnoses (Tarver, 2012). Lung cancer accounts for more deaths than any other cancer in both men and women. An estimated 158,080 deaths are expected to occur in 2016, accounting for about 1 in 4 cancer deaths. The 5-year survival rate for small cell lung cancer (7%) is lower than that for NSCLC (21%) (Tarver, 2012).

Improvement of glucose control remains one of the central goals of effective diabetes management, which aims to reduce morbidity and mortality by decreasing the risk of diabetes-associated complications (Tarver, 2012). A vast number of factors are considered by clinicians and patients when selecting adequate pharmacologic diabetes therapies. Various classes of diabetes drugs operate at different parts of this glucose–insulin pathway. This may include increases in insulin secreted by the pancreas, increases of the sensitivity to insulin by target organs, and decrease the rate at which glucose is absorbed by the gastrointestinal tract (Kahn, 2005).

Metformin is a part of the biguanide class of oral hypoglycemic agents and is a regularly prescribed medication for various conditions including diabetes, polycystic ovary syndrome (Nestler, 2008) and non-alcoholic fatty liver disease (Marchesini, 2005). For T2D, it is the first-line drug of choice among patients with normal kidney function (Nathan, 2009). The primary mechanism of operation is thought to be primarily via decreased hepatic glucose output by

inhibition of gluconeogenesis, with a secondary drop in insulin levels, with no major effects on insulin signaling. Furthermore, an 'average' individual with T2D has three times the normal rate of gluconeogenesis, thus, metformin treatment reduces this by more than one-third (Hundal, 2000).

Diabetes treatments may influence the risk, development and cancer prognosis when it develops. There is epidemiologic and pathophysiologic evidence that metformin may have a protective effect for NSCLC patients. Our objective is to investigate the impact metformin and other antidiabetic drug medications have on survival of diabetic NSCLC patients.

Methods

Data Source

This is retrospective database study utilized the linked cancer registry data and Medicare claims from the SEER - Medicare linked database. The SEER – Medicare linked databases provided a temporal view of patients with T2D and NSCLC (2007 - 2013). The SEER program collects information incident cancer diagnosis within a defined geographic area. The program originated in 1973, now includes registries that cover about 26 percent of the U.S. population (Warne, 2002). There is vast information captured in the database including patient's age, race, sex, and marital status. Information about cancer includes the month and year of diagnosis, behavior, the site, and stage. Moreover, there is also staging information in the SEER data which is based on a classification that can vary by cancer site as well as year of diagnosis (Warne, 2002).

Study Population

Patients were included in the study if they were diagnosed with NSCLC between January 01, 2008 and December 31, 2013, at least 66 years old, continuous enrollment in Medicare A and B in the 12 months prior to diagnosis. Patients were excluded if their date of death recorded was prior to or in the same month of diagnosis and if they were enrolled in an HMO at any time during the 12 months prior to diagnosis, as complete claims for these patients were unavailable.

NSCLC diagnosis was based on the International Classification of Disease for Oncology (3rd edition, ICD-O-3) histology codes in the SEER Medicare data. Tumor stage was classified according to the 6th edition of the American Joint Commission on Cancer. Diagnosis of preexisting T2D in NSCLC patients was identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) 250.xx prior to cancer diagnosis utilizing Medicare claims files. The cohort was restricted to patients who did not receive any antidiabetic medication for at least 90 days prior to diabetes diagnosis.

For both cases and controls incident medication was defined as patients that did have a claim for an anti-diabetic drug medication 90-days preceding the 1st observed claim of an anti-diabetic drug. Cases were defined as incident metformin user and may be combination therapy users, after initial metformin utilization. Controls were defined as incident users of other anti-diabetic drug medications (Dipipeptidyl peptidase 4 (DPP-4), Sulfonylurea and Thiazolidinedione. The date of cohort entry was defined as the date of incident antidiabetic drug medication. Cases and controls were matched on their propensity score at a 3:1 ratio (Parsons, 2004).

A secondary analysis of incident antidiabetic drug utilization defined as patients that did not have a claim for an anti-diabetic drug medication 90-days preceding the 1st observed claim of an anti-diabetic drug, after NSCLC diagnosis. Cases were defined as incident metformin user and may be combination therapy users, after initial metformin utilization. Controls were defined as incident users of other anti-diabetic drug medications (Dipipeptidyl peptidase 4 (DPP-4), Sulfonylurea and Thiazolidinedione. The date of cohort entry was defined as the date of incident antidiabetic drug medication Cases and controls were then matched on their propensity score at a 1:1 ratio (Parsons, 2004). The secondary analysis assessed the impact of incident metformin utilization on NSCLC, however, it is inherently biased by immortal time bias. This is because patients must be alive to receive their first prescription of medication (Matok, 2014).

Statistical Analysis

Descriptive statistics were utilized to summarize demographic and clinical characteristics by metformin and other anti-diabetic users. Differences between groups were assessed using chi-square test for categorical and t tests for continuous variables, prior to matching. After matching both groups, Standardized differences were calculated to assess the balance between the metformin and other antidiabetic drug medication groups, with values greater than 0.2 indicating imbalance. Overall survival was measured from date of incident metformin or other ADM to NSCLC diagnosis date. In the overall survival analysis, comparisons were made between NSCLC patients with diabetes and for all stages of cancer. Kaplan Meier and log rank tests were used to examine overall survival for cases and controls. Multivariable survival analysis was completed by cox proportional hazard model. Cox proportional hazards models were used to predict progression to NSCLC adjusted for baseline demographics (age, sex, and race/ethnicity). Statistical significance was established at $P<0.05$. The effects of cumulative duration of exposure to antidiabetic medication was assessed by using a Cox proportional hazard model. To avoid survival bias (ie, those who take metformin longer are obviously those who survive longer), all cumulative drug exposures after NSCLC diagnosis were modeled as time-dependent covariates.

However, findings from the Kaplan Meier survival analysis, primary and secondary analysis, displayed crossing hazard lines. This violates the assumptions of survival analysis and subsequent analyses such as Cox proportional hazards regression and log-rank test will either lose power or be rendered inadequate. Therefore, to adequately analyze survival data with crossing hazard rates the Renyi test statistic was utilized (Davis, 2011).

Statistical significance was set at $P\leq 0.05$. SAS 9.4 (SAS Institute Inc, Cary, North Carolina) was used for all data analyses. This study was approved by National Cancer Institute and the Institutional Review Board at the University of North Carolina at Charlotte.

Results

In the primary analysis, we identified 4, 652 patients aged older than 66 years with T2D prior to diagnosis of NSCLC. Of these T2D NSCLC patients 692 were incident metformin users and 161 were incident other anti-diabetic drug medication users. Prior to matching metformin users and other antidiabetic drug medication users were similar in age (73.7 years versus 74.5 years, respectively). There were not any statistical differences in gender, race, stage, mortality or geographic variation. Differences in comorbidities between the metformin and other ADM users, included significantly greater hypothyroidism, per-vascular disorder, renal failure, congestive heart failure and arrhythmias ($p<0.05$) (Table 3.0). Patients included in the other ADM group had significantly higher CCI score 6.12(3.28) compared to metformin (mono or combination therapy users) ($p<0.001$). After matching, 400 beneficiaries were assigned to cases (n = 300) and controls (n = 100). Differences in comorbidities were less apparent (using the standardized mean difference) (Table 3.1).

The overall median survival was not significantly different in the metformin NSCLC group (1334 days) compared to the other ADM NSCLC group (1134 days; Renyi test statistic $p<0.5784$) (Figure 2.0).

In the secondary analysis, we identified 4, 652 patients aged older than 66 years with T2D prior to diagnosis of NSCLC. Of these patients 312 were incident metformin users and 111 were incident other anti-diabetic drug medication users, after their NSCLC diagnosis. Prior to matching both groups, patients without there were no statistical differences in demographic characteristics. Differences in comorbidities between the groups included significantly higher congestive heart failure, arrhythmias, and pulmonary circulation disorder ($P < 0.001$) (Table 3.2). After matching, 196 beneficiaries were assigned to cases (n = 98) and controls (n = 98). Differences in comorbidities were less apparent (using the standardized mean difference) (Table 3.3).

The overall median survival was longer in the Metformin NSCLC group (384 days) compared to the other ADM NSCLC group (428.5 days; Renyi test statistic $p<0.4925$) (Figure 2.1).

Discussion

This retrospective observational study showed that diabetic NSCLC patients on metformin did not have a difference in survival compared to other antidiabetic drug medication patients.

These results are similar to the results of two retrospective cohort studies. These studies found no association between the use of metformin and survival in patients with NSCLC (Kowall, 2015; Mc Menamin, 2016). Similarly, in a prospective, randomized, open-label, controlled pilot study conducted on patients with stage IV NSCLC, metformin administration reduced occurrence of chemotherapy induced-nausea but did not statistically improve the objective response rate or overall survival (Sayed, 2015). Metformin had no effect on NSCLC despite differences in design, such as cancer stage, chemotherapy regime, and use of placebo, this clinical trial showed a consistent null effect of metformin on survival in patients with advanced NSCLC.

One prior study has shown an anticancer effect of metformin in patients with diabetes with stage IV NSCLC taking metformin versus those not on metformin, however the study design was subject to prevalent user bias. Lin et al (2015) utilized data from the Surveillance, Epidemiology, and End Results registry linked to Medicare claims and identified 750 patients with diabetes 65–80 years of age diagnosed with stage IV NSCLC between 2007 and 2009. Authors reported that at the time of NSCLC diagnosis, 61% of patients were on metformin. The metformin group had a median survival of 5 months, compared with 3 months in patients not treated with metformin ($P < 0.001$). Additionally, results showed statistically significant improvement in survival (hazard ratio, 0.80; 95% confidence interval, 0.71–0.89) for metformin patients, after controlling for various factors, diabetes severity, cancer characteristics, other

diabetes medications, and treatment. However, a main limitation of this study is that authors assessed prevalent use of metformin and therefore this is subject to prevalent user bias. Prevalent users had to be alive in order to use the drug. Therefore use of metformin would have altered various risk factors (Yang, 2014).

In the current study, findings of no association between metformin and NSCLC may be attributed to the highly comorbid population that has been assessed. The vast number of comorbidities may have been an effect modifier impacting the association. Previous literature has indicated that in studies with 1–5 years of follow-up, mortality in patients with lung cancer is 1.1 to 1.5 times higher for those with comorbidity (Tammemagi, 2003; Janssen-Heijnen, 2007; Battafarano, 2002). Survival for NSCLC patients with severe comorbidities may also impact treatment as studies have reported surgical resection has 25%–58% lower odds in lung cancer patients with severe comorbidity compared with patients without comorbidity (Lüchtenborg, 2012; Cykert, 2010). Moreover, many studies have shown that comorbidity is associated with decreased likelihood of completion of chemotherapy (Grønberg, 2010). Additionally, the findings from this study may only be generalizable to patients that are over the age of 66 years old. This is a highly comorbid population, especially patients with prevalent T2D. Previous literature indicates that the most comorbid ailments are associated with age (Piccirillo, 2008). Therefore, within this population the benefit of metformin use may be outweighed by multiple comorbidities. Two clinical trials enrolled patients with type 2 diabetes and patients that were older than 60 years old did not appear to have a benefit from metformin (Diabetes Prevention Program Research Group, 2002; Crandall, 2006). Further confirming age, and increased comorbidity associated with age, may affect patient's opportunity to benefit from metformin.

In summary, we did not observe a survival benefit from metformin use in NSCLC patients over the age of 66 years old, suggesting that comorbidity may hinder the effectiveness of metformin.

Conclusion

Findings from this retrospective observational study demonstrate that diabetic NSCLC patients on metformin did not have a difference in survival compared to other antidiabetic drug medication patients. Oncologists should consider that comorbidity management will play an increasing role in health services, and healthcare providers and researchers must assess the complexity of managing and studying patients with complex medication conditions.

While findings of this aim present there is null results, science is, by its nature, is a highly collaborative discipline, and thus presenting null results allows colleagues to not unnecessarily use time and resources to repeat our findings. Additionally, this study highlights that if future research is conducted with the patient population, there is need for a more robust dataset that can consider various confounding factors that may impact the association between metformin and NSCLC.

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CHAPTER 5 TABLES

Table 5.0 - Patient Characteristics of T2D NSCLC Patients on Metformin versus Other Antidiabetic Drug Medication (Prior to Matching)

	Metformin (Mono or Combo) (n=692)		Other ADM Users (excluding insulin) (n=161)		
	N	**%**	**N**	**%**	**P-Value**
Age at Cancer Diagnosis					0.021
Age 65-69	145	21%	20	12%	
Age 70-74	222	32%	51	32%	
Age 75-79	161	23%	39	24%	
Age 80-84	114	16%	29	18%	
Age 85+	50	7%	22	14%	
Age at Cancer Diagnosis					0.329
Mean	76.52		74.89		
SD	6.37		6.05		
Gender					0.530
Male	350	51%	77	48%	
Female	342	49%	84	52%	
Race/ Ethnicity					0.217
White	625	90%	138	86%	
Black	36	5%	14	9%	
American Indian/Alaska Native	3	<1%	0	<1%	
Asian or Pacific Islander	28	4%	9	6%	
Stage of Diagnosis					0.895
Stage I	225	33%	49	30%	
Stage II	42	6%	10	6%	
Stage IIIA	45	7%	14	9%	
Stage IIIB	98	14%	23	14%	
Stage IV	282	41%	65	40%	
Mortality (% Dead)	533	77%	130	81%	0.307
Geographic Area					0.665
San Francisco-Oakland	13	2%	7	4%	
Connecticut	33	5%	8	5%	
Metropolitan	49	7%	7	4%	
Hawaii	8	1%	3	2%	
Iowa	37	5%	11	7%	
New	8	1%	1	1%	
Seattle	33	5%	6	4%	
Utah	7	1%	1	1%	
Atlanta	15	2%	4	2%	
Alaska	0	0%		0%	

San Jose- Monterey	13	2%	2	1%	
Los Angeles	32	5%	8	5%	
Georgia	1	<1%	0	<1%	
Greater California	105	15%	20	12%	
Kentucky	86	12%	17	11%	
Louisiana	43	6%	8	5%	
New Jersey	139	20%	45	28%	
Georgia	70	10%	13	8%	
Elixhauser					
Alcohol abuse	10	1%	3	2%	0.696
Blood loss anemia	21	3%	2	1%	0.206
Arrhythmias	201	29%	61	38%	0.029
Congestive heart failure	48	7%	21	13%	0.011
Coagulopathy	12	2%	2	1%	0.658
COPD	378	55%	93	58%	0.471
Deficiency anemia	68	10%	21	13%	0.229
Depression	66	10%	19	12%	0.388
Drug Abuse	3	<1%	1	1%	0.754
HIV/AIDS	1	0%	0	0%	0.629
Hypothyroidism	5	1%	9	6%	<.0001
Liver disease	50	7%	16	10%	0.246
Lymphoma	12	2%	4	2%	0.527
Obesity	63	9%	13	8%	0.680
Other neurological disorders	46	7%	12	7%	0.714
Paralysis	1	<1%	0	0%	0.629
Peptic ulcer no bleed	15	2%	7	4%	0.116
Peri-Vascular disorder	92	13%	42	26%	<.0001
Psychoses	4	1%	1	1%	0.949
Pulmonary circulation disorder	19	3%	7	4%	0.287
Renal failure	16	2%	24	15%	<.0001
Rheumatoid arthritis	18	3%	6	4%	0.437
Nonmetastatic tumor	19	3%	5	3%	0.804
Valvular Disease	16	2%	6	4%	0.308
Weight Loss	66	10%	18	11%	0.529
CCI					<.0001
Mean	4.83		6.17		
Median	4.00		6.00		
SD	3.20		3.28		

CCI = Charleston Comorbidity Index; COPD =Chronic Obstructive Pulmonary Disorder; SD= Standard Deviation

Table 5.1 – Patient Characteristics of T2D NSCLC Patients on Metformin versus Other Antidiabetic Drug Medication (Post Matching)

	Metformin (Mono or Combo) (n=300)		**Other ADM Users (excluding insulin) (n=100)**		
	N	**%**	**N**	**%**	**Standardized Difference***
Age at Cancer Diagnosis					0.110
Age 66-69	45	15%	18	18%	
Age 70-74	112	37%	33	33%	
Age 75-79	78	26%	26	26%	
Age 80-84	38	13%	14	14%	
Age 85+	27	9%	9	9%	
Age at Cancer Diagnosis					0.002
Mean	75.22		75.19		
SD	5.89		6.04		
Gender					0.041
Male	161	54%	44	44%	
Female	139	46%	56	56%	
Race/ Ethnicity					0.131
White	45	15%	18	18%	
Black	112	37%	33	33%	
American Indian/Alaska Native	78	26%	26	26%	
Asian or Pacific Islander	38	13%	14	14%	
Other unspecified	27	9%	9	9%	
Stage of Diagnosis					0.127
Stage I	102	34%	34	34%	
Stage II	15	5%	7	7%	
Stage IIIA	23	8%	9	9%	
Stage IIIB	44	15%	16	16%	
Stage IV	116	39%	34	34%	
Mortality (% Dead)	235	78%	77	77%	0.032
Geographic Area					0.401
San Francisco-Oakland	6	2%	4	4%	
Connecticut	14	5%	4	4%	
Metropolitan	24	8%	4	4%	
Hawaii	1	0%	2	2%	
Iowa	15	5%	8	8%	
New	2	1%	1	1%	
Seattle	16	5%	5	5%	
Atlanta	7	2%	2	2%	
Alaska	0	0%	2	2%	
San Jose- Monterey	7	2%	0	0%	
Los Angeles	17	6%	5	5%	

Georgia	1	<1%	0	0%	
Greater California	48	16%	11	11%	
Kentucky	40	13%	14	14%	
Louisiana	19	6%	4	4%	
New Jersey	53	18%	26	26%	
Georgia	30	10%	8	8%	
Elixhauser					
Alcohol abuse	4	1%	3	3%	0.048
Blood loss anemia	11	4%	1	1%	0.130
Arrhythmias	98	33%	36	36%	0.107
Congestive heart failure	25	8%	10	10%	0.058
Coagulopathy	3	1%	1	1%	0.095
COPD	179	60%	59	59%	0.071
Deficiency anemia	35	12%	10	10%	0.127
Depression	29	10%	12	12%	0.066
Drug Abuse	0	0%	1	1%	0.003
HIV/AIDS	1	<1%	0	0%	0.150
Hypertension Uncomplicated	0	0%	0	0%	0.098
Hypothyroidism	1	0%	1	1%	0.076
Liver disease	24	8%	7	7%	0.054
Lymphoma	6	2%	2	2%	0.088
Obesity	26	9%	7	7%	0.165
Other neurological disorders	22	7%	6	6%	0.088
Peptic ulcer no bleed	11	4%	3	3%	0.140
Peri-Vascular disorder	41	14%	19	19%	0.181
Psychoses	3	1%	0	0%	0.099
Pulmonary circulation disorder	10	3%	5	5%	0.123
Renal failure	3	1%	0	0%	0.198
Rheumatoid arthritis	9	3%	3	3%	0.027
Nonmetastatic tumor	11	4%	2	2%	0.054
Valvular Disease	11	4%	5	5%	0.179
Weight Loss	30	10%	7	7%	0.024
CCI					
Mean	5.89		5.17		0.231
Median	5.00		5.00		
SD	3.27		2.90		

CCI = Charleston Comorbidity Index; COPD =Chronic Obstructive Pulmonary Disorder; SD= Standard Deviation

* Standardized difference = difference in means or proportions divided by standard error; imbalance defined as value greater than 0.20 (small effect size).

Table 5.2 - Patient Characteristics of T2D NSCLC Patients on Metformin versus Other Antidiabetic Drug Medication (Prior to Matching)

	Metformin (Mono or Combo) (n=312)		**Other ADM Users (excluding insulin) (n=111)**		
		312		**111**	
	N	**%**	**N**	**%**	**P Value**
Age at Cancer Diagnosis					0.725
Age 65-69	85	27%	31	28%	
Age 70-74	93	30%	29	26%	
Age 75-79	86	28%	28	25%	
Age 80-84	31	10%	14	13%	
Age 85+	17	5%	9	8%	
Age at Cancer Diagnosis					0.813
Mean	73.75		74.56		
SD	5.70		6.36		
Gender					0.937
Male	170	54%	60	54%	
Female	142	46%	51	46%	
Race/ Ethnicity					0.976
White	272	87%	96	86%	
Black	24	8%	9	8%	
American Indian/Alaska Native	1	<1%	0	0%	
Asian or Pacific Islander	13	4%	5	5%	
Other unspecified	2	1%	1	1%	
Stage of Diagnosis					0.957
Stage I	148	47%	50	45%	
Stage II	24	8%	10	9%	
Stage IIIA	20	6%	9	8%	
Stage IIIB	44	14%	16	14%	
Stage IV	76	24%	26	23%	
Mortality (% Dead)	194	62%	79	71%	0.089
Geographic Area					0.791
San Francisco-Oakland	6	2%	2	2%	
Connecticut	15	5%	9	8%	
Metropolitan	26	8%	11	10%	
Hawaii	5	2%	3	3%	
Iowa	13	4%	7	6%	
New	8	3%	0	0%	
Seattle	15	5%	2	2%	
Utah	4	1%	1	1%	
Atlanta	9	3%	2	2%	
San Jose- Monterey	5	2%	2	2%	
Los Angeles	15	5%	5	5%	

Georgia	3	1%	0	0%	
Greater California	42	13%	12	11%	
Kentucky	41	13%	12	11%	
Louisiana	13	4%	4	4%	
New Jersey	67	21%	27	24%	
Georgia	25	8%	12	11%	
Elixhauser					
Alcohol abuse	6	2%	4	4%	0.317
Blood loss anemia	9	3%	6	5%	0.218
Arrhythmias	78	25%	42	38%	0.010
Congestive heart failure	16	5%	12	11%	0.039
Coagulopathy	6	2%	0	0%	0.141
COPD	158	51%	59	53%	0.649
Deficiency anemia	26	8%	14	13%	0.186
Depression	23	7%	11	10%	0.843
Drug Abuse	3	1%	0	0%	0.300
Fluid and electrolyte disorders	1	<1%	0	0%	0.550
HIV/AIDS	1	<1%	0	0%	0.550
Hypertension Complicated	0	0%	0	0%	0.000
Hypothyroidism	4	1%	1	1%	0.750
Liver disease	24	8%	9	8%	0.888
Lymphoma	4	1%	0	0%	0.231
Obesity	25	8%	11	10%	0.538
Other neurological disorders	17	5%	6	5%	0.986
Paralysis	1	<1%	1	1%	0.444
Peptic ulcer no bleed	5	2%	1	1%	0.591
Peri-Vascular disorder	43	14%	20	18%	0.282
Psychoses	1	<1%	1	1%	0.444
Pulmonary circulation disorder	4	1%	6	5%	0.014
Renal failure	6	2%	16	14%	<.0001
Rheumatoid arthritis	5	2%	3	3%	0.465
Nonmetastatic tumor	12	4%	1	1%	0.123
Valvular Disease	4	1%	4	4%	0.123
Weight Loss	21	7%	8	7%	0.865
CCI					0.001
Mean	4.28		5.41		
Median	4.00		5.00		
SD	2.56		3.29		

CCI = Charleston Comorbidity Index; COPD =Chronic Obstructive Pulmonary Disorder; SD= Standard Deviation

Table 5.3 – Patient Characteristics of T2D NSCLC Patients on Metformin versus Other Antidiabetic Drug Medication (Post Matching)

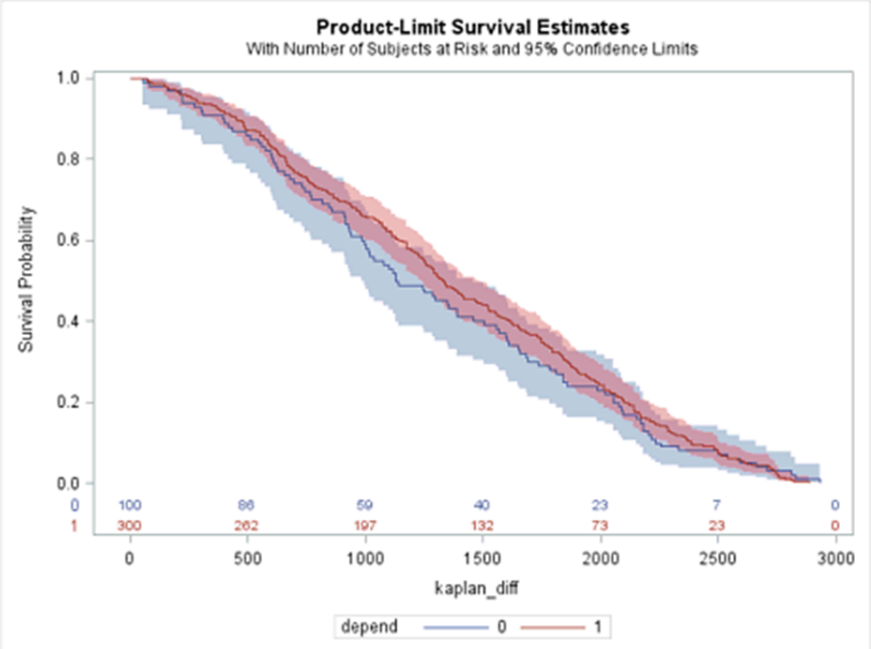
	Metformin (Mono or Combo) (n=98)		Other ADM Users (excluding insulin) (n=98)		
	N	**%**	**N**	**%**	**Standardized Difference***
Age at Cancer Diagnosis					0.0961
Age 65-69	24	24%	27	28%	
Age 70-74	31	32%	27	28%	
Age 75-79	27	28%	25	26%	
Age 80-84	11	11%	12	12%	
Age 85+	5	5%	7	7%	
Age at Cancer Diagnosis					0.0643
Mean	73.84		75.59		
SD	5.40		6.52		
Gender					0.1521
Male	57	58%	51	52%	
Female	41	42%	47	48%	
Race/ Ethnicity					0.0800
White	82	84%	84	86%	
Black	9	9%	9	9%	
American Indian/Alaska Native	1	1%	0	0%	
Asian or Pacific Islander	6	6%	4	4%	
Other unspecified	0	0%	1	1%	
Stage of Diagnosis					0.1651
Stage I	41	42%	44	45%	
Stage II	7	7%	9	9%	
Stage IIIA	4	4%	8	8%	
Stage IIIB	13	13%	13	13%	
Stage IV	33	34%	24	24%	
Mortality (% Dead)	70	71%	69	70%	0.0588
Geographic Area					0.1159
San Francisco-Oakland	0	0%	2	2%	
Connecticut	15	15%	9	9%	
Metropolitan	24	24%	10	10%	
Hawaii	4	4%	2	2%	
Iowa	10	10%	7	7%	
New	7	7%	0	0%	
Seattle	9	9%	2	2%	
Utah	2	2%	1	1%	
Atlanta	0	0%	2	2%	
San Jose- Monterey	1	1%	2	2%	
Los Angeles	1	1%	5	5%	

Greater California	2	2%	10	10%	
Kentucky	12	12%	11	11%	
Louisiana	3	3%	2	2%	
New Jersey	6	6%	23	23%	
Georgia	2	2%	10	10%	
Elixhauser					
Alcohol abuse	3	3%	4	4%	0.1520
Blood loss anemia	2	2%	3	3%	0.0647
Arrhythmias	27	28%	32	33%	0.0816
Congestive heart failure	6	6%	9	9%	0.1804
Coagulopathy	1	1%	0	0%	0.0073
COPD	42	43%	51	52%	0.0914
Deficiency anemia	5	5%	10	10%	0.0949
Depression	9	9%	9	9%	0.0549
Hypothyroidism	0	0%	1	1%	0.1960
Liver disease	11	11%	8	8%	0.1350
Lymphoma	1	1%	0	0%	0.1372
Obesity	8	8%	7	7%	0.1557
Other neurological disorders	7	7%	5	5%	0.0279
Paralysis	1	1%	0	0%	0.0879
Peptic ulcer no bleed	1	1%	0	0%	0.0437
Peri-Vascular disorder	10	10%	17	17%	0.0856
Pulmonary circulation disorder	4	4%	4	4%	0.1976
Renal failure	6	6%	5	5%	0.1350
Rheumatoid arthritis	0	0%	2	2%	0.0086
Nonmetastatic tumor	4	4%	1	1%	0.0942
Valvular Disease	2	2%	3	3%	0.1482
Weight Loss	7	7%	7	7%	0.1941
CCI					0.0894
Mean	4.74		5.13		
Median	4.00		4.00		
SD	3.03		3.354		

CCI = Charleston Comorbidity Index; COPD =Chronic Obstructive Pulmonary Disorder; SD= Standard Deviation

* Standardized difference = difference in means or proportions divided by standard error; imbalance defined as value greater than 0.20 (small effect size).

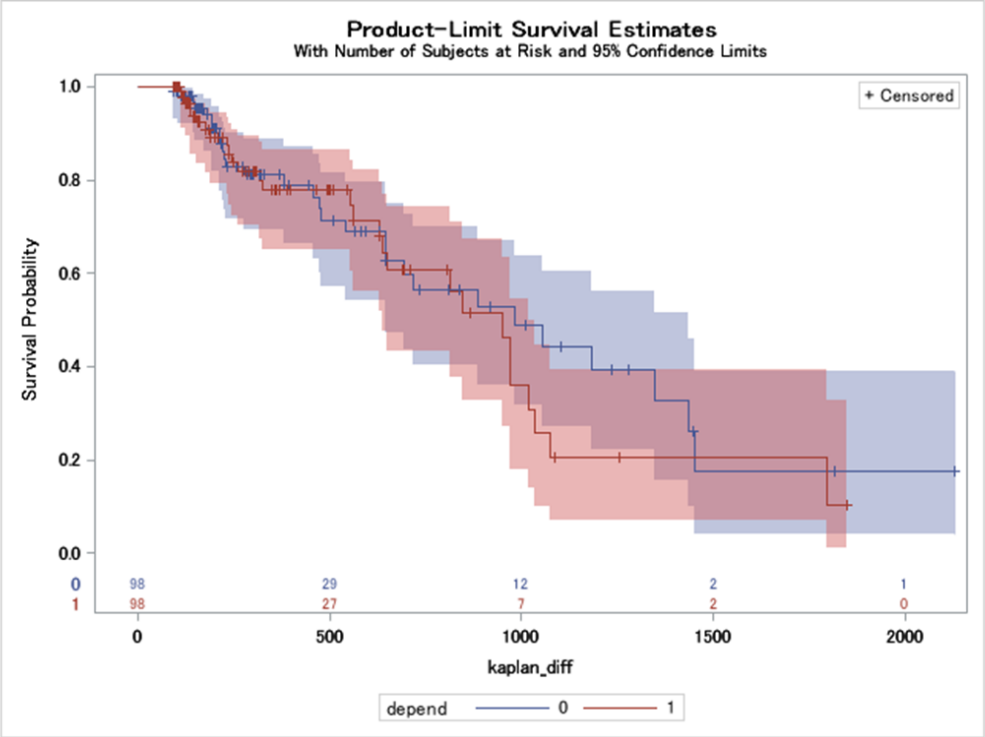
CHAPTER 5 FIGURES



Group	Total	Dead	Alive Censored	Percent Alive	Mean Days	Median Days
Metformin (1)	300	235	65	22%	1390.14	1334.50
Other ADM (0)	100	77	23	23%	1297.90	1134.00

Renyi test statistic = 0.5784

Figure 5.0 – Kaplan Meier Survival Analysis of Diabetic NSCLC Patients on Metformin versus Patients on Other Antidiabetic Drug Medication



Group	Total	Dead	Alive Censored	Percent Alive	Mean Days	Median Days
Metformin (1)	98	70	28	25.6%	535.97	384.00
Other ADM (0)	98	69	29	29.6%	553.48	428.50

Renyi test statistic = 0.7716

Figure 5.1 – Kaplan Meier Survival Analysis of Diabetic NSCLC Patients on Metformin versus Patients on Other Antidiabetic Drug Medication – Secondary Analysis

Chapter 6: Discussion and Conclusion

6.1 Conclusion

This retrospective analysis conducted with the SEER Medicare linked dataset within NSCLC patients illustrates healthcare costs as well as utilization within this population and the impact of diabetes and metformin utilization on survival and time to NSCLC diagnosis. This dissertation established the ability to assess time to NSCLC diagnosis and death as well as healthcare cost and utilization, in a population that would be typically underrepresented in clinical trials. Key findings from this study indicate that: healthcare cost and utilization for diabetic NSCLC patients is heighted in specific settings, compared to NSCLC patients and incident metformin users have increased time to NSCLC diagnosis compared to other antidiabetic drug users, incident metformin users have greater time to NSCLC diagnosis, and there are no differences in survival for incident metformin NSCLC patients compared to other antidiabetic drug medication users.

6.2 Implications for policy and practice

This study has vast implications for policy and practice given that the US spends approximately 16% (which is equivalent to greater than $2 trillion) of its gross domestic product on health care (Keehan, 2008). Cancer care accounts for almost 5% of health care spending, and this proportion is expected to increase (The National Cancer Institute Costs of cancer care, n.d). According to National Institutes of Health estimates, that $89 billion was spent on cancer care in 2007, with the economic burden totaling $219.2 billion (this included indirect costs associated with lost productivity and death) (American Cancer Society, 2008). Recent trends indicate that cancer spending growth will upsurge, in part as a result of costly new treatments and the escalate in the number of cancer patients as the population ages (Hoffman, 2008). Currently, there is no preventative strategy for NSCLC, and findings from this study indicate Metformin may decrease time to NSCLC diagnosis.

Oncologists should be aware of the potential interaction of T2D antidiabetic drug medication and the subsequent risk associated, compared to the general population. This does not translate into more intensive cancer screening; rather, there is evidence that patients with T2D underutilization national screening programs. Additionally, among diabetes patients that develop cancer, treatment and outcomes may be impacted. However, this relationship must be further quantified. From the diabetes point of view, there is no call for changes to clinical practice, in terms of prescribing ADM medication. Physicians across oncology and diabetes must be conscious of patients' medication history. Additionally, researchers across both the diabetes and cancer communities must continue to collaborate, design clinical trials and explore the interaction of these two diseases. Journal editors must also be aware of the methodological drawbacks associated with studies that assess the interaction and draw on unbiased interpretations.

This dissertation will provide further data to understand the interaction of Metformin and NSCLC. Prior to implementation, this dissertation can serve as proof of concept to inform further exploration of the relationship between metformin and NSCLC through rodent models and long term randomized control trials. Moreover, understanding the principal mechanisms by which metformin works can help potentially develop novel treatments for cancer patients. However, in order to truly understand the pharmacological effect of metformin on risk of NSCLC, it would be ideal to conduct a randomized control trial where patients are randomized to metformin or diet only. This would allow for patients initiating metformin with those controlling their disease by only diet, while adjusting for disease severity. Moreover, this will allow for controlling time dependent confounders affected by previous treatment and thus, can provide valuable insights.

There are many new research questions that have emerged through this dissertation process. It is essential that future research assess the influence of diabetes and smoking history on survival among NSCLC patients. Future research should also consider the complexity and heterogeneity of older adults. When researchers assess an older population multiple comorbidities and geriatric syndromes should be considered. Moreover, specific study designs

should also be considered when researchers would like to study older adults with NSCLC. Randomized control trials typically do not include older adults, over the age of 65 years old, with multiple comorbidities. Therefore, advanced observational or comparative effectiveness evidence from a real-world setting may prove to be more beneficial for this population.

Furthermore, additional data from electronic health records (EHRs), would play a valuable role. Claims data are advantageous for collecting data from various sites of services that may not be included in a single EHR and, consequently, allow for improved risk classification of a patient and analysis of overall utilization of health services. However, EHRs, on the other hand, contain valuable clinical detail not found in claims records and generally include data spanning multiple payers. Future studies should include patients' caner progression and utilize current data to assess healthcare utilization, treatment patterns and cost, given the rapid addition of novel cancer treatments. The addition of more clinical data in addition to claims data will provide a more robust picture of the various factors impacting outcomes as well as patients' interaction with the healthcare system.

There may be various forms of data that can be utilized further explore findings of this dissertation however, the patient population of interest, limitations of the data and risk factors that may impact the disease must be considered carefully.

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