Prevalence of Heart Disease and Diabetes in Individuals with Lung Cancer

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A Senior Honors Project Presented to the

Honors College

East Carolina University

In Partial Fulfillment of the

Requirements for

Graduation with Honors

by

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Greenville, NC

May 2020

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Cardiovascular disease (CVD), type 2 diabetes mellitus (DM2) and lung cancer are the leading causes of death in the United States annually (ACS Facts and Figures, 2018; CDC Heart Disease Facts and Statistics, 2018). Lung cancer accounts for 30% of all new cases of cancer in the state of North Carolina, with nearly 6,000 new cases being diagnosed annually (ACS Facts and Figures, 2018). CVD was responsible for the deaths of nearly 19,000 North Carolinians in 2017 alone (Centers for Disease Control and Prevention, 2018). Diabetes incidence is consistently higher in North Carolina than the national average of 10.5%; 11.4% of adult North Carolinians have diabetes, this number increases to 18.6% when looking at more rural regions such as Eastern North Carolina (ENC) (United Health Foundation, 2019).

Higher incidence of lung cancer has been demonstrated in populations with DM2 or CVD (Al-Kindi, & Oliveira 2016; Davis, Rajala, Tyldesley, Pickles, &Virani, 2015). Al-Kindi and Oliveira found that 41% of lung cancer patients have a concurrent CVD diagnosis (2016). CVD is an umbrella term for many conditions such as hypertension, coronary artery disease, carotid artery disease, peripheral vascular disease, cerebrovascular accident, and heart failure (Al-Kindi & Oliveira, 2016). Of these, lung cancer patients are most likely to be impacted by Hyperlipidemia, (HLD) or hypertension (HTN) (Kravchenko et al., 2015). Patients with diabetes, especially DM2 have been shown to have higher overall incidence of lung and other cancers than their non-diabetic counterparts (Giovannucci et al., 2010; Ruban et al., 2017). The presence of these diagnoses is often associated with a worse overall prognosis due to the higher levels of complications in those with lung cancer and complex comorbidities (Rivera et al., 2019; Ruban et al., 2017).

The risk factors for CVD, DM2, and lung cancer have considerable overlap (Giovannucci et al., 2010; Johnson, Davis, Law, & Sulpher, 2016). However, little known research examines how these medical conditions may influence one another or health outcomes, especially in diverse populations. Behaviors such as smoking tobacco products, high body mass index (BMI), poor diet, and low levels of activity have been cited to increase the risk for development of all of these conditions (Davis et al., 2015; Hermann et al., 2014; Luo, Hendryx, Qi, Ho, & Margolis, 2016). Such risk factors are especially common in the rural south where the use of tobacco products is widespread (ACS Facts and Figures, 2016; Islam, Jiang, Anggondowati, Lin & Ganti, 2015; Underwood, 2012). Compounding the influence of these risk factors, rural regions such as ENC oftentimes have decreased access to high quality local healthcare, which can allow for further disease development or progression before intervention (Caldwell. Ford, Wallace, Wang, & Takahashi, 2016). This scarcity of care resources can impair an individual's likelihood of receiving early screening and treatment (Nadpara, Madhavan, & Tworek, 2016). In fact, less than half of individuals who live in rural and medically sparse areas, such as much of ENC, receive treatment adhering to current guideline recommendations for lung cancer (Nadpara et al., 2016). Additionally, African Americans with lung cancer living in rural areas experience higher premature death rates than their urban counterparts (Singh & Jemal, 2017).

In 2004, the American Diabetes Association, the American Cancer Society, and the American Heart Association published a scientific statement calling for more effective preventive health care, targeting shared risk factors for these three important diseases (Johnson et al, 2016). The prevalence of cardiovascular complications related to the care of cancer is

predicted to increase in coming years (Sueta, & Hokimoto, 2016). With this in mind, this study hopes to highlight incidence of CVD and DM2 experienced by individuals with lung cancer.

Literature Review

Development of Conditions

Relationships between pre-existing CVD or DM2 have been associated with the development of cancers. This is largely due to the overlapping risk factors such as smoking, poor diet, and exercise that are shared between these diseases (Davis, et al., 2015; Hermann et al., 2014; Luo et al., 2016). Evidence has shown that these risk factors associated with CVD and DM2 development are related to not only increased incidence of cancer but also "excess cancer mortality" (Johnson et al., 2016). However, CVD alone has been shown to triple an individual's risk of cancer development regardless of smoking history (Hatlen, Langhammer, Carlsen, Salvesen, Amundsen, 2014). The reason for this is credited to the chronic inflammation experienced by both patient populations (Hermann et al., 2014). For those with DM2, this inflammation combined with the state of hyperinsulinemia is hypothesized to be responsible for not only the development of cancer but progression of the disease into a worse prognosis (Davis et al., 2015; Giovannucci et al., 2010).

Complications

Beyond the development of cancer in those with CVD and DM2, these individuals are oftentimes faced with poorer overall prognosis. These complex-comorbidities may influence the development of further comorbidities (Islam et al., 2015; Johnson et al., 2016). Specifically, patients with DM2 have an increased risk for higher levels of comorbidity development when compared to those without diabetes, which ultimately leads to higher mortality rates (Ruban et al., 2017). Preexisting CVDs have been shown to create a synergistic negative effect on overall

mortality rate for individuals with lung cancer when receiving treatment such as surgery, chemotherapy or radiotherapy (Kravchenko et al., 2015). Individuals with CVD are also more likely to experience more distant metastatic sites (Rivera et al., 2019) leading to higher mortality rates for individuals in nearly every stage of cancer (Kravchenko et al., 2015). It is proposed that the development of these metastasis is due to the chronic inflammation experienced by those with CVD (Rivera et al., 2019). These individuals tend to take daily medications to combat the negative effects of these conditions, however, many of these medications have been shown to impact the antineoplastic effects of the cancer treatments used in lung cancer patients.

Treatment Impact on Outlook

Medications used for the management of CVD and DM2 have been shown to play a role in the patient outcomes related not only to their chronic conditions but also their cancer (Giovannucci et al., 2010; Kravchenko et al., 2015; Xu T. et al., 2015). It is important to identify the influence of these medications to better tailor oncologic management options for this population. Those with DM2 typically manage their illness with oral medications, however more serious cases may indicate the need for insulin administration. Metformin is the most common of the oral medications taken by those with DM2 (Giovannucci et al., 2010). Individuals who take metformin have been shown to have an overall lower mortality than their counterparts that take other medications (Xu T. et al.,, 2015). Metformin has shown the ability to cause cell cycle arrest in cancer cells, which plays a role in risk minimization of tumor growth in individuals also experiencing hyperinsulinemia (Giovannucci et al., 2010). With worsening DM2, some patients may need to use insulin to manage blood glucose levels. This subcutaneous injection of insulin raises levels of circulating insulin in the body. Prolonged insulin use combined with increased

insulin resistance have been shown to increase patient mortality due to insulin binding to IGF-1 receptors (Davis et al., 2015; Giovannucci et al., 2010).

The most common forms of CVD seen in patients with cancer are HTN and HLD. These conditions have demonstrated protective effects on overall cancer prognosis when compared to individuals with cancer and other forms of CVD (Kravchenko et al., 2015). This is reported to be due to the beneficial effects of medications used for these conditions such as ACE inhibitors and Statins (Kravchenko et al., 2015). However, congestive heart failure and arrhythmias have been shown to play a negative impact on prognosis for those receiving surgical or radiation therapy (Kravchenko et al., 2015). Arrhythmias and heart failure are both relatively common in those with lung cancer, both as preexisting conditions and following treatment of cancer (Kravchenko et al., 2015). While advancement in the treatment of malignancies has advanced significantly in recent years, adverse effects on the cardiovascular system, such as arrhythmias and heart failure, play a large role in the negative prognosis and quality of life found in this population (Sueta, & Hokimoto, 2016). Many therapeutic agents indicated in the treatment of lung cancer, such as, cisplatin, anthracyclines, melphalan, 5-Fu, and dispeptide, have demonstrated such cardiotoxic effects (Kravchenko et al., 2015), which can ultimately place limitations on the “selection and tolerance” of available therapeutic modalities for individuals with CVD (Kravchenko et al., 2015). Despite these findings of potential complications, only half of those with cancer and CVD are referred to cardiology consultation or receive guideline approved therapy (Al-Kindi & Oliveira, 2016). This highlights the importance of appropriate research into this up and coming topic.

Research Question

The purpose of this study was to examine the prevalence of CVD and DM2 in adults with lung cancer in ENC.

- **Aim 1**: Describe the prevalence of CVD in individuals with lung cancer in ENC.
- **Aim 2**: Describe the prevalence of DM2 in individuals with lung cancer in ENC.
- **Aim 3**: Describe the prevalence of CVD and DM2 in individuals with lung cancer by race.

Methods

A retrospective chart review was conducted to identify the prevalence of complex comorbidities among a geographically and racially diverse sample of individuals with lung cancer. This study was approved by the Institutional Review Board (IRB) of the affiliated university and hospital system.

Procedures

Following IRB approval, participants were identified through a list generated by the cancer registry of a larger tertiary oncology center and its satellite oncology treatment sites located in ENC. Data was extracted from electronic health records (EHRs) of new patient visits for non-small-cell lung cancer occurring at the tertiary medical center or an affiliated treatment center between January 1, 2015 and June 30, 2016. This study is a secondary analysis.

To be included in the study, an individual must be 1) at least 18 years old, 2) have a histologically proven diagnosis of lung cancer, and 3) have attended a new patient visit between January 1, 2015 and June 30, 2016 in the medical oncology clinic. Participants with any other active cancer other than lung cancer were not included in the study.

Data Collection

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at East Carolina University. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources (Harris et al., 2009; Harris et al., 2019).

Sociodemographic data collected included age, gender, race, ethnicity, zip code, relationship status, insurance coverage, and smoking history. Past medical history collected included stage of disease at diagnosis and CVD or DM2 diagnosis.

Definitions

Using the 2013 National Center for Health Statistics Urban-Rural Classification Scheme for Counties (US Department of Health & Human Services, 2013), zip codes were classified into rural and urban counties. Noncore and micropolitan counties were coded as rural counties while small metro, medium metro, large fringe metro, and large central metro counties were coded as urban. For the purposes of this study CVD was defined in accordance with that used in Al-Kindi and Oliveira's 2017 study. Only those with a documented diagnosis of hypertension, coronary artery disease, carotid artery disease, peripheral vascular disease, cerebrovascular accident, and heart failure were considered to have a CVD.

Data Analysis

SPSS v24.0 statistical analysis software provided by East Carolina University was used to analyze this data. Descriptive statistics were used to analyze data.

Results

Most subjects (N=380) were male (59%) and married (47%). The mean age was 68 years (SD = 10.4). The diversity of the sample is representative of the regional population: 33% were Black and 53% lived in a federally designated rural county. In this sample, 93% had a smoking history. The most prevalent primary insurance for this sample was Medicare (72%) followed by Medicaid (27%). See demographical information in Table 1.

Table 1

Demographic Data

	Mean	SD
Age	71.8	10.4
	%	n
Insurance Type		
Medicare	71.5	271
Medicaid	26.8	102
Marital Status		
Single	27.5	104
Single living with partner	1.6	6
Married	47.1	178
Widowed	18.0	68
Other	4.5	17
Missing	1.3	5
Race		
White	66.5	250
Black	32.7	123
Other	0.8	3
Gender		
Male	58.6	222
Female	41.4	157
Residence		
Rural	52.9	201
Urban	47.2	179
Smoking History		
Smoker	92.6	349
Nonsmoker	7.4	28

May not equal total sample due to missing data

In this sample, 76% had at least one documented CVD diagnosis. Of those with CVD, 48% had more than once concurrent CVD diagnosis. (See Figure 1). 79% of the sample had diagnosed CVD and 29% had diagnosed DM2. Prevalence rates for CVD were as follows: hypertension (76%), coronary artery disease (22%), carotid artery disease (3%), peripheral vascular disease (10%), cerebrovascular accident (14%), heart failure (14%) (See Figure 2).

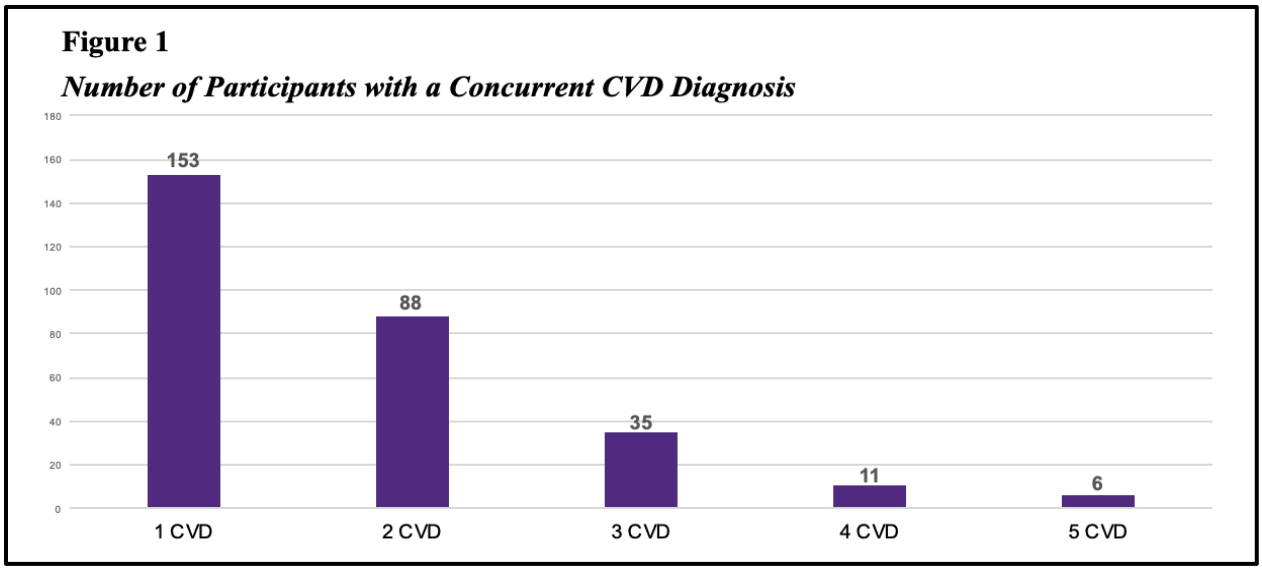

Figure 1. Demonstrates the number of participants with multiple CVD diagnoses

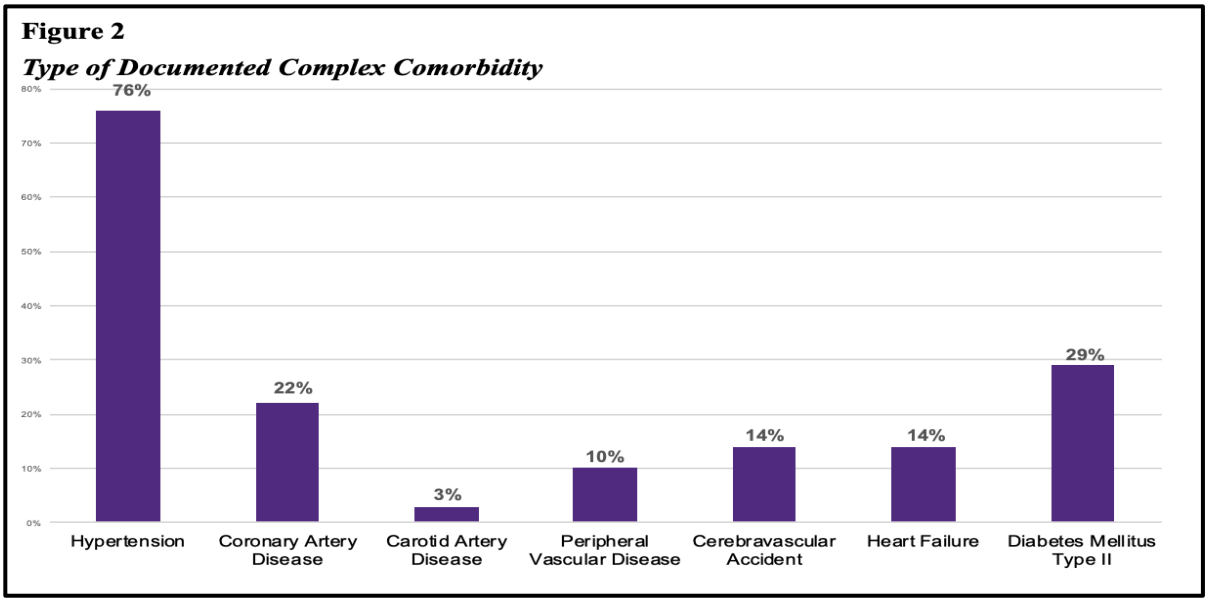

Figure 2. shows the percent of the sample with each type of CVD or DM2

78% of White and Black participants had some form of CVD. With roughly 40% of each group having 2 or more concurrent diagnoses. Of those with diagnosed CVD, Coronary Artery Disease was more prevalent among Whites, with 24% having documented diagnosis, whereas only 13% was noted among Blacks. DM2 impacted 37% of Black participants, and only 26% of White participants. Rates of Hypertension were 76% and 73% for Black and White participants respectively. This is notably higher than the national average of 33% (Centers for Disease Control, 2016). (See Table 2)

Table 2

Complex-Comorbidities by Race

	Black (n=123)		White (n=246)	
	%	n	%	n
Any CVD	78.0	96	77.6	194
Total CVD				
0	19.5	24	20.8	52
1	41.5	51	40.0	100
2	23.6	29	23.2	58
3	8.1	10	10.0	25
4	2.4	3	3.2	8
5	1.6	2	1.2	3
Hypertension	76.4	94	72.8	180
Coronary Artery Disease	13.0	16	23.6	59
Carotid Artery Disease	2.4	3	4.0	10
Peripheral Vascular Disease	10.6	13	8.8	22
Cerebral Vascular Accident/Stroke	14.6	18	12.8	32
Heart Failure	14.6	18	14.0	35
DM2	36.6	45	26.0	65

May not equal total sample due to missing data

Discussion

This retrospective chart review identified the prevalence of complex comorbidities, CVD and DM2, in individuals with lung cancer. Prevalence of complex comorbidities was further examined by race. This is the first known study to examine these complex comorbidities in individuals with lung cancer in ENC. The study sample was racially diverse and is representative of the local population, including both rural dwellers and low-income individuals. The local population is racially diverse: 59% of the population is White and 35% of the population is Black (U.S. Census Bureau, 2019). The sample in this study had a relatively similar distribution of race. The mean household income of this county is $44,315 annually, and 23.3% of the residents live in poverty (U.S. Census Bureau, 2019). Although we did not collect income as part of this study, many participants had either Medicare or Medicaid insurance, indicating the socioeconomic status of the sample was representative of the region.

Results showed the majority of participants were diagnosed with CVD. The prevalence of CVD in our study was 78%. This is higher than previously reported results by Al-Kindi and Oliveira's study in which only 43% of individuals with lung cancer were diagnosed with CVD (2016). Within the lung cancer sample included in Al-Kindi and Oliveira's study, the findings of prevalence for specific types of CVD were comparable to our sample for coronary artery disease, carotid artery disease, heart failure, and cerebrovascular accident. Their study found a much higher prevalence of peripheral vascular disease with diagnosis in 28% of their lung cancer cohort whereas it was diagnosed in only 10% of this sample. However, their study did not examine the prevalence of HTN or total number of CVD diagnoses which we found to be quite numerous in this sample of individuals with lung cancer.

This study found a prevalence rate of 36% for DM2. The rate in our study is higher than a similar study in which 30% of a sample of individuals with non-small cell lung cancer were diagnosed with DM2 prior to a cancer diagnosis (Ruban et al., 2017). In another study conducted in Japan, the incidence of diabetes mellitus within their sample was 19% (Kurishima et al., 2017). According to Giovannucci et al., patients with DM2 are often at an increased risk of developing certain cancers (2010). Some studies have shown that the presence of DM2 in an individual with lung cancer may negatively impact prognosis as it has been associated with higher rates of mortality (Kurishima et al., 2017; Ruban et al., 2017; Zhu et al., 2016). This has been attributed the presence of hyperinsulinemia as well as the impact of various treatment modalities for DM2 (Giovannucci et al., 2010).

The findings of this study shed a unique light on the prevalence of complex comorbidities in individuals with lung cancer, particularly those living in the rural south. This may be attributed to the common risk factors shared by lung cancer, CVD, and DM2 including smoking, poor diet, lack of exercise and obesity (Johnson et al., 2016). Such health behaviors are especially prevalent in the regions of the rural south such as ENC, which serves to highlight the importance of education to promote positive health behaviors in an effort to prevent the development of these conditions.

In recent years, rural areas have experienced increases in diversity: 80% of rural population growth is attributed to minorities (Johnson, 2012). Minorities, especially those in rural areas, are more likely to be diagnosed with late stage lung cancer and not receive appropriate referrals or guideline-based care. These disparities are attributed to limited access to medical care, as well as being less likely to receive cancer screening, and timely treatment (Nadpara et al., 2016). This study identified that beyond the risk this group faces for not

receiving the appropriate care once diagnosed, minorities with lung cancer also face a high likelihood of being diagnosed with complex-comorbidity, which can further limit their treatment options and impact outcomes.

Understanding regional patterns and variations in lung cancer, CVD, and DM2 can help practitioners understand which individuals with lung cancer may be most at risk for experiencing complex comorbidities. Practitioners should consider taking a more holistic approach in the assessment of patients with lung cancer. Despite the potential for improved patient quality of life, relief of symptoms, and care giver burden identified in the use of palliative care, it is utilized less often in rurally residing individuals with cancer than their urban counterparts (Bakitas et al., 2020). Health care providers should take into account the presence of these racial and regional disparities when examining these patients as well as the presence of these diagnoses when prescribing palliative care services. Despite the overlap in risk factors, the clinical manifestations of lung cancer, CVD, and DM2 vary greatly and should be all be considered when addressing supportive and comfort focused treatments for this patient population to promote patient quality of life. It is important to begin to consider comprehensive palliative care programs that are designed to address complex comorbidities rather than a single disease.

Limitations

Due to the retrospective nature of this study we were unable to determine the exact influence of CVD and DM2 on treatment options and patient outcomes. This study did not examine the differences in treatment or medication usage in clients with complex comorbidity and their counterparts. Finally, this was a cross sectional study which prevented us from following patient outcomes after the point of data-collection.

Future Directions

Future studies can further examine the influence of complex comorbidity on patient reported symptoms, outcomes, and overall survival as compared to those without complex comorbidities. Investigations regarding the most effective treatment modalities to manage the symptoms associated with CVD, DM2, and concurrent lung cancer as well as improve patient outcomes should be conducted. More research is needed to determine the role CVD and DM2 may have in lung cancer disparities and how these comorbidities intersect in underserved populations.

Implications for Nursing

Comorbid conditions, such as CVD or DM2, may influence the disease trajectory or treatment options for those with lung cancer. Disparities in access to quality healthcare have been noted on a geographical, gender, and racial basis. These variations in access to care, along with CVD and DM2 comorbidities, should be considered when caring for underserved populations with lung cancer. Nurses should assess patients for symptoms beyond just cancer symptoms and make recommendations or institute appropriate interventions accordingly. The nurse should educate clients of available palliative care options to manage symptoms and improve quality of life. Palliative care intervention should be designed and tailored to address individual care needs for individuals with multiple complex comorbidities.

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