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Pancreatic Cancer: Quantitative Study Investigating the Regional Risk Factors in North Carolina

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Walden University
2022

Abstract

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by

Holly Marie Myers

MS, Wake Forest University, 2004

BA, Catawba College, 2000

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health – Epidemiology

Walden University

February 2023

Abstract

Pancreatic cancer is the fourth-leading cause of cancer-related deaths in the United States, killing more than 90% of individuals diagnosed within 5 years. Due to the lack of signs and symptoms, 82% of all pancreatic cancer cases are diagnosed in terminal stages. As such, the most powerful method to reducing the morbidity and mortality of pancreatic cancer is to further investigate the risk factors. According to the theoretical framework of the ecosocial theory, long-term exposure to exposures to unfavorable socioecological and environmental factors serve as a "web of causation" for adverse health outcomes. Using data from the North Carolina Department of Health and Human Services (NCDHHS), Environmental Protection Agency (EPA), and Unites States Geological Society (USGS), these studies investigated the regional societostructural/ medical and environmental risk factors for pancreatic cancer in North Carolina. Using a random sampling (*n*=1,200) of pancreatic cancer patients, logistic regression and Kruskal-Wallis analyses showed significant, regional differences in societostructural/medical and environmental risk factors among North Carolina pancreatic cancer patients. Furthermore, it was noted that the accumulation of the largest number of risk factors coincided with the region of North Carolina with the highest incidence of pancreatic cancer. As such, medical professionals in North Carolina have a better understanding of the regional risk factors that influence pancreatic cancer within their communities. As the incidence of pancreatic cancer continues to grow, the investigation of pancreatic cancer risk factors presents a viable opportunity to reduce the mortality and morbidity associated with the disease.

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Dedication

Imagine waking up tomorrow and finding out that you or a loved one only had 6 months to live. In June of 2019, my family received this news. My stepfather, who is generally very healthy, was diagnosed with pancreatic cancer at the age of 62. His diagnosis resulted in my desire to understand the causes of pancreatic cancer and why incidence rates continue to rise in North Carolina. Following surgery to remove the head of the pancreas, duodenum, and biliary system (Whipple procedure) and rounds of both chemotherapy and radiation therapy, my stepfather was one of the lucky 10.8%. As of today, his CA19-9 levels continue to remain low and PET scans do not show reoccurrence. But many other North Carolinians are not as lucky. As such, these studies are dedicated to the individuals and families who have battled pancreatic cancer, especially Bryan Scyphers (my stepfather), Don Phillips (pastor and husband of a coworker), and Mike Lambros (North Davidson High School softball coach).

Acknowledgments

"Sometimes people come into your life for a moment, day, or a lifetime. It matters not the time they spent with you but how they impacted your life in that time."

- Unknown

First, I would like to acknowledge Mrs. Barbara Teal, my high school science teacher. She embodied a genuine passion for science, learning, and discovery – and had a lot of fun doing it! Her enthusiasm continues to resonate with me to this day and has always served as a foundation for my continued journey to explore science. Secondly, I'd like to acknowledge to impact of Dr. John Wear, former executive director for the Center for the Environment at Catawba College. Dr. Wear worked tirelessly to provide education and outreach on prevalent environmental challenges in the community. His efforts provided a basis for my inspiration to investigate environmental issues and how they impact overall health. I would also like to acknowledge Dr. Darryl Nevels, my classmate and dear friend. His friendship and support have been critical, and I would not have made it without him. Lastly, I'd like to acknowledge the support of my friends and family. Pursuing a doctorate degree as a single parent working full-time in their 40s isn't easy. But with the support and patience of my mother and stepfather (Marsha Myers and Bryan Scyphers), father (Bobby Myers), Dennis Buice (partner), children (Bentley and Parker Weir), siblings (Travis Myers and Wendy Gentrup), and supportive coworkers at Davidson-Davie Community College, I have been able to achieve my dream of getting a Ph.D.

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Part 1: Overview

Introduction

Though rare, pancreatic cancer is resistant to established therapies and is associated with a bleak prognosis for survival (David et al., 2019; U.S. Preventive Services Task Force, 2019). Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States (Maisonneuve, 2019) and has a 5-year survival rate of 9.3% (Rawla et al., 2019; Ward et al., 2019). Patients diagnosed with pancreatic cancer face an average life expectancy of 6 to 24 months (David et al., 2019). Due to challenges associated with the early detection of pancreatic cancer (Henrikson et al., 2019), 82% of the cases are often diagnosed in malignant stages (Surveillance, Epidemiology, and End Results Program [SEER], n.d.-a.). Given this, identification of risk factors is an optimal approach to reducing the mortality associated with pancreatic cancer.

Since 2006, the incidence and mortality of pancreatic cancer has increased annually (American Cancer Society [ACS], 2019). Pancreatic cancer is more common in older adults, with 90% of cases diagnosed after the age of 55 (Ilic & Ilic, 2016). Pancreatic cancer is slightly more common in males with higher incidence rates among African American and White races (Idachaba et al., 2019).

Problem Statement

Histologically, pancreatic cancer is characterized into endocrine and exocrine-based tumors (ACS, 2021). Endocrine-based tumors constitute less that 5% of all pancreatic cancers and often have a better prognosis of survival while exocrine-based tumors, such as adenocarcinoma and ampullary carcinoma, have deadlier outcomes (Johns Hopkins Medicine, 2021). Due to the physical location and physiological function of the pancreas, pancreatic cancer produces minimal, vague symptoms (Mizrahi et al., 2020). Symptoms often occur after the tumor has grown large and metastasized to surrounding organs (John Hopkins Medicine, 2021). Factors that influence the type and severity of symptoms include the type of cancer and location of the tumor within the pancreas (Gobbi et al., 2013; Tang et al., 2018). While abdominal pain is the most common symptom of all pancreatic cancers, tumors located in the head of the pancreas often block the flow of pancreatic juice, producing symptoms such as jaundice, weight loss, and steatorrhea (Sattar et al., 2019). Tumors located in the body and tail of the pancreas can also produce nausea, vomiting, bloating, new-onset diabetes, lethargy, changes in bowel habits, and pain in the back and shoulders (Sattar et al., 2019; Tang et al., 2018).

The burden of pancreatic cancer in North Carolina has increased from 10.3 cases per 100,000 in 1999 to 13.1 cases per 100,000 in 2017 (Centers for Disease Control and Prevention [CDC], n.d.). Specifically, in western North Carolina (the mountain region), 21 of the 23 counties (91%) are at or below the current pancreatic cancer rate, while two counties (9%) have pancreatic cancer rates above the state average (National Cancer Institute [NCI], 2020). Contrastingly, approximately 41% of the counties in the piedmont and coastal plains region are above the state average (NCI, 2020). Epidemiological trends of pancreatic cancer vary greatly (Maisonneuve, 2019), suggesting that variations in the exposure to societostructural/medical and environmental risk factors might explain the regional variations observed (GBD 2017 Pancreatic Cancer Collaborators, 2019; Soliman et al., 2006). While similar studies have been conducted in other geographic locations (Brotherton et al., 2016; Neuberger et al., 2004; Velean et al., 2018), such investigations focusing on North Carolina have not been performed. A review of the literature found that societostructural/medical and environmental risks associated with pancreatic cancer in North Carolina is grossly understudied, implying a possible gap in literature-based evidence surrounding the associations between pancreatic cancer and environmental risk factors. This suggests a need for this research project and a potential opportunity for an informed social change through the data analyzed.

Purpose of the Study

The purpose of these studies was to identify the relationship between societostructural/medical and environmental risk factors and regional variations in pancreatic cancer in North Carolina. Societostructural/medical and environmental risk factors are associated with the occurrence of pancreatic cancer (Coss et al., 2004; Koivusalo et al., 1994). Using available secondary data sources, these studies examined associations between regional level rates of societostructural factors, such as gender, age, race, and income, medical risk factors such as smoking and relevant past medical history, as well as environmental factors, such as air and water quality, and the occurrence of pancreatic cancer.

Framework

The theoretical framework associated with these studies is the ecosocial theory. First termed by Nancy Kriegger in 1994, the ecosocial theory provides a foundation for understanding how exposures to unfavorable socioecological and environmental factors serve as a "web of causation" for adverse health outcomes. Specifically, this theory postulates that observed health disparities in at-risk populations are the biological manifestation of differential exposures to adverse social, political, economic, and environmental factors (Honojo, 2004; Krieger, 2012; Wemrell et al., 2016). This theory is similar to other multifactoral models, such as the socioecological theory, expanding to integrate the concepts of molecular and cellular biology, observational and experimental research, pathology, and epidemiology (Krieger, 2001).

One unique aspect of the ecosocial theory is the concept of embodiment: "how we literally incorporate, biologically, in a societal and ecological context, the material and social world in which we live" (Krieger, 2012). Krieger (2012) adds that pathways of embodiment can include adverse exposure to economic and social deprivation, hazardous substances, social trauma, targeted marketing of harmful products (i.e., tobacco products), unequal access to health resources, and degradations to ecosystems. This theory states that health cannot be explained by disease mechanism alone and postulates that determinants of disease patterns are intricately associated with the social and physical environments in which people live (Krieger, 2001), which offers insight into why regional variations of pancreatic cancer would exist in North Carolina.

Social Impact

This study focused on pancreatic cancer trends in North Carolina, providing local healthcare providers with insight as to how sociostructural and environmental risk factors may influence the prevalence of pancreatic cancer in their communities. Numerous studies document the deadly and aggressive nature of pancreatic cancer (Khalaf et al., 2021; Latenstein et al, 2020). More importantly, trends of pancreatic cancer incidence are growing globally (Chen et al., 2020; Henley et al., 2020), with pancreatic cancer expected to become the second deadliest cancer-related death by 2030 (Rahib et al., 2014). Despite this, early detection of pancreatic cancer has yet to be solved, causing the U.S. Preventative Task Force to recommend against routine screening in asymptomatic adults (Henrikson et al., 2019). Furthermore, pancreatic cancer shows significant resistance to conventional chemotherapeutic and radiotherapeutic treatments (David et al., 2019).

As such, the most powerful tool to combat pancreatic cancer is to further investigate how societostructural/medical and environmental risk factors influence pancreatic cancer. While previous studies have provided statistical evidence of associations between risk factors and the occurrence of pancreatic cancer, health care providers may not understand how those factors are associated with pancreatic cancer in their own communities. Results from this study will identify associations between the incidence of pancreatic cancer and localized societal, medical, and environmental risk factors. This research and potential findings can support social change by allowing healthcare providers to create contextualized approaches to preventing pancreatic cancer within their communities.

Background

Historical Findings

A review of the literature shows that hundreds of peer-reviewed articles are written detailing novel epidemiological findings in pancreatic cancer each year. As such, knowledge about associations between risk factors and pancreatic cancer continue to emerge. In the United States, SEER (n.d.-a.) estimates more than 57,000 pancreatic cancer cases will occur in 2020, ranking 11th and constituting approximately 3.2% of all cancer cases. Despite this, pancreatic cancer is the 3rd highest cause of cancer-related death (ACS, 2021). Patients diagnosed with pancreatic cancer have a 10% chance of surviving, excluding deaths from all other causes (SEER, n.d.-a.). The nationwide incidence rate of pancreatic cancer is 13.1 cases per 100,000 individuals (SEER, n.d.-a.). While pancreatic cancer is more common in males (Henrikson et al., 2019), there is no statistically significant difference in the incidence, prevalence, and mortality among gender (Lippi & Mattiuzzi, 2020). Pancreatic cancer incidence rates are highest in individuals aged 65-74, with the median age at diagnosis of 70 (SEER, n.d.-a.).

In the United States, the burden of pancreatic cancer is is highest in African American and Caucasian populations and lowest among Asian and Pacific Islanders (SEER, n.d.-a.). Many studies have found that the burden of pancreatic cancer (incidence, prevalence, disability-adjusted life years [DALYs], and mortality) is significantly positively correlated with socio-demographic index (SDI) values (GBD 2017 Pancreatic

Cancer Collaborators, 2019; Lippi & Mattiuzzi, 2020; Maisonneuve, 2019). For example, Lippi and Mattiuzzi (2020) found that incidence of pancreatic cancer ranged from 13 cases per million in low SDI populations, gradually increasing to 185 cases per million in high SDI populations ($r = 0.993$, $p < 0.01$). This regional variability of pancratic cancer burden suggests that there is variability in the exposure of individuals to risk factors, making the content of these studies critical in public health efforts to reduce the burden of pancreatic cancer.

Societostructural/Medical Risk Factor for Pancreatic Cancer

A review of the literature indicate that the majority of focus around analyzing pancreatic cancer risk factors lies in the societostructural/medical category. Several studies found increased risk of pancreatic cancer associated with smoking in their study population (Huang et al., 2019; Pang et al., 2018). Risk estimates of developing pancreatic cancer ranged from 1.45 (Pang et al., 2018) to 11.83 (Hao et al., 2017) when compared to individuals who did not smoke. The study by Hao et al. (2017) examined the risk for pancreatic cancer in a study population of individuals with a history of pancreatitis, which is a known risk factor for pancreatic cancer. Therefore, the observed risk estimate may be confounded by the additional risk of pancreatic cancer. Excluding the study by Hao et al., the risk estimate of developing pancreatic cancer associated with smoking averaged 2.18, indicating that smokers are approximately 2 times more likely to develop pancreatic cancer than non-smokers.

The second-most studied societostructural/medical risk factor studied was previous diagnosis with diabetes. As with smoking, all studies that calculated risk estimates associated with diabetes found significant increased risks of developing pancreatic cancer in their study populations (Setiawan et al., 2018; Zheng et al., 2016). The risk estimates ranged from 1.32 in a multiethnic cohort (Huang et al., 2019) to 7.70 in Latino individuals aged 65 and older (Setiawan et al., 2018). Many studies documented the risk estimate differential between individuals with recently diagnosed diabetes and those who have had diabetes for longer than 2 years. For example, in a study population of 1,200 patients with pancreatic adenocarcinoma, Pang et al. (2017) found that individuals diagnosed with diabetes for less than 2 years had 2.43 increased odds of developing pancreatic cancer when compared to those without diabetes. When diabetes was diagnosed between 2-5 years and 5 years, the odds of developing pancreatic cancer was 1.72 and 1.98, respectively (Pang et al., 2017). Similar studies were conducted by Setiawan et al. (2018), showing not only increased odds associated with recent diagnosis of pancreatic cancer, but also in a racial/ethnic subset.

Studies investigating gender and familial history returned significant findings. Specifically, studies conducted by Andersson et al. (2016), Pang et al. (2017), and Wang et al. (2018) found slight increased odds of developing pancreatic cancer by gender. In these studies, increased odds were noted in females (Andersson et al, 2016; Wang et al., 2018) with increased odds for males noted in the study conducted by Pang et al. (2017). Presence of a familial history of pancreatic cancer and previous diagnosis with pancreatitis was significantly associated with increased risk estimate of pancreatic cancer in all studies that were investigates. Two studies (Huang et al., 2019; Zheng et al., 2019) identified significant increased risk of pancreatic cancer associated with the presence of more than two first-degree relatives diagnosed with pancreatic cancer (RR = 1.97, OR = 2.11, and OR = 1.23, respectively).

Studies by Huang et al. (2019) and Setiawan et al. (2018) investigated associations of pancreatic cancer and race/ethnicity. Both studies returned significant risk estimates associated with race/ethnic backgrounds and pancreatic cancer. After adjusting for known risk factors, Huang et al. found that Native Hawaiians, Japanese Americans, and African Americans had higher risk of pancreatic cancer as compared to European Americans, but not Latino American. Similarly, after adjusting for both age and diabetes status, Setiawan et al. found that both African American and Latinos had significantly higher odds (HR = 5.49, HR = 7.70, respectively).

Two studies (Chen et al., 2020; Wong et al., 2017) found that regions with higher SDI values had significantly higher levels of incidence and mortality associated with pancreatic cancer than regions with lower SDI values. Furthermore, studies have documented the association between increased age and pancreatic cancer (Lippi & Mattiuzzi, 2020).

Environmental Risk Factors of Pancreatic Cancer

Exposure to chemicals was highlighted as the most well-studied environmental risk factor, producing strong evidence for the inclusion of pesticides and insecticides as risk factors for pancreatic cancer. Associations between direct and indirect exposure to agricultural pesiticides and pancreatic cancer were somewhat inconclusive. Studies conducted by Antwi et al. (2015), and Kachuri et al. (2017) found significant risk estimates associated with pancreatic cancer and direct exposure (OR = 1.21 and HR = 1.36, respectively), while Louis et al. (2017) found significant risk estimates associated with pancreatic cancer and indirect exposure to lindane (OR = 3.7) but failed to find significant associations between pancreatic cancer and DDT and chlordane in female spouses of pesticide applicators. However, Fritschi et al. (2015) did not find significant associations between pancreatic cancer and exposures to pesticides or *N*–nitrosamines.

Studies that investigated associations between pollution in rural and urban settings and pancreatic cancer found significant associations. Specifically, Wang et al. (2018) found that $PM_{2.5}$ air pollition was significantly, slightly associated with increased risk of pancreatic cancer, with risk increases along with age and urbanicity. Additionally, Baum et al. (2020) found that when controlling for age, individuals living in urban regions were 1.3 times more likely to develop pancreatic cancer than those living in rural areas.

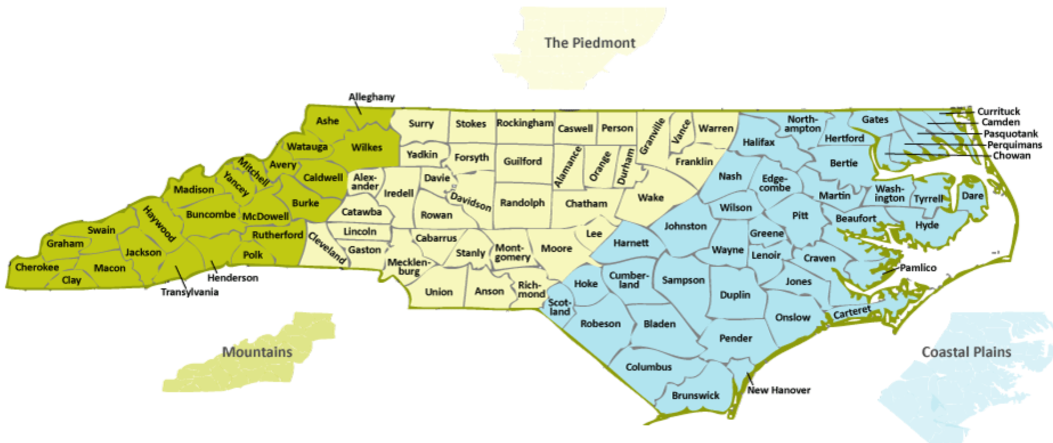
In a study conducted by Antwi et al. (2015), significant associations between pancreatic cancer and regular exposure to asbestos (OR=1.54), benzene (OR=1.70), and chlorinated hydrocarbons (OR=1.63) were associated with an increased risk in pancreatic cancer while exposure to chromium and nickel were not associated with pancreatic cancer. Grigorescu et al. (2018) found that individuals exposed to occupational chemicals (such as diesel) were 6.28 times more likely to develop pancreatic cancer. Lastly, Mastrantonio et al., (2018) did not find significant associations between poor water quality and pancreatic cancer. Unfortunately, due to the lack of available literature, additional measures of environmental risk factors cannot be decided in the scope of this literature review.

Overview of the Manuscripts

The three studies that follow investigated the associations between pancreatic cancer and societostructural/medical and environmental risk factors. The goal of these studies was to identify regional differences in risk of pancreatic cancer. The regional designation for each study aligned with the major geographic regions of North Carolina: mountains, piedmont, and coastal plains (Figure 1). A list of the region designated for each county can be found in Appendix A. Using secondary data sources, these studies focused on the incidence of pancreatic cancer in North Carolina. The first manuscript focused on societostructural/medical risk factors while the second and third manuscript focused on environmental risk factors (air quality and water quality, respectively).

Figure 1

Major Geographic Regions of North Carolina



Note: Adapted from *Our State Geography in a Snap: Three Regions Overview*, by the North Carolina Department of Public Instruction, 2012 (https://www.dpi.nc.gov). In the public domain.

Manuscript 1

This quantitative study investigated the association between societostructural/medical risk factors and pancreatic cancer in North Carolina.

Research Question

To what extent is there an association between regional levels of societostructural/medical risk factors and pancreatic cancer in North Carolina?

Null hypothesis. There is not an association between regional levels of societostructural/medical risk factors and pancreatic cancer in North Carolina.

Alternate hypothesis. There is an association between regional levels of societostructural/medical risk factors and pancreatic cancer in North Carolina.

Nature of the Study

This study implemented a cross-sectional study design using a quantitative approach to understand the associations between regional risk factors of pancreatic cancer. All data were retrospectively obtained from the North Carolina Central Cancer Registry (NCCCR) following established procedures for data release of partially identifiable cancer data. Prevalent pancreatic cancer cases of patients aged 18 years or older residing within the state between January 1, 2010, and December 31, 2020, were included. Using the county, the patient resided in at diagnosis, study participants were coded to one of the regions of North Carolina: mountain, piedmont, or coastal plains. Variables associated with insurance, primary cancer site, race, sex, and history of tobacco use were recoded into categorical variables. To investigate the relationship between the three regions, dummy bivariate categorical variables for the three regions were created. Chi-square test of independence and logistic regression analyses were completed to examine the relationship between the research variables.

Limitations, Challenges, and Barriers

The cross-sectional study design provided a snapshot of the outcome of interest and the potential risk factors, allowing researchers to provide a description of the outcome of interest during the given timeframe (Levin, 2006). As such, the results of this study cannot provide temporal or causal associations between risk factors and the outcome of interest (Sedgwick, 2014).

Manuscript 2

This quantitative study investigated the association between air quality risk factors and pancreatic cancer in North Carolina.

Research Question

To what extent is there an association between regional air quality levels and pancreatic cancer in North Carolina?

Null hypothesis. There is not an association between regional air quality levels and pancreatic cancer in North Carolina.

Alternate hypothesis. There is an association between regional air quality levels and pancreatic cancer in North Carolina.

Nature of the Study

This study implemented a cross-sectional study design using a quantitative approach. All data were retrospectively obtained from the North Carolina Central Cancer Registry (NCCCR) following established procedures for data release of partially identifiable cancer data. Prevalent pancreatic cancer cases of patients aged 18 years or older residing within the state between January 1, 2010, and December 31, 2020, were included. Using the county the patient resided in at diagnosis, study participants were coded to one of the regions of North Carolina: mountain, piedmont, or coastal plains.

Air quality data was obtained for 122 air quality factors from the Environmental Protection Agency (EPA) for relevant air quality factors between January 1, 2000, and December 31, 2020, providing 1,653,342 total data points. After review of the air quality data and current literature around the carcinogenic propensity of air quality factors, 11 variables were selected for inclusion in the study. Twenty-year means were calculated for each county in which the air quality factor was monitored. The mean value for each air quality factor was added to each patient record that resided in that county upon diagnosis. Given the non-parametric nature of the data, Kruskal-Wallis analyses were completed to examine the relationship between the research variables.

Limitations, Challenges, and Barriers

Air quality factors are not actively monitored in all 100 counties of North Carolina. As such, the regional averages for each air quality factor represents the average of only those counties within that region that monitor these factors. Additionally, it was noted that counties in the mountain region had a lower amount of air quality monitoring stations than those in the piedmont and coastal plains. As such, regional differences may be associated with the differential monitoring practices of the North Carolina Department of Environmental Quality. Furthermore, the cross-sectional study design provided a snapshot of the outcome of interest and the potential risk factors, allowing researchers to provide a description of the outcome of interest during the given timeframe (Levin, 2006). As such, the results of this study cannot provide temporal or causal associations between risk factors and the outcome of interest (Sedgwick, 2014).

Manuscript 3

This quantitative study investigated the association between water quality risk factors and pancreatic cancer in North Carolina.

Research Question

To what extent is there an association between regional water quality levels and pancreatic cancer in North Carolina?

Null hypothesis. There is not an association between regional water quality levels and pancreatic cancer in North Carolina.

Alternate hypothesis. There is an association between regional water quality levels and pancreatic cancer in North Carolina.

Nature of the Study

This study implemented a cross-sectional study design using a quantitative approach. All data were retrospectively obtained from the NCCCR following established procedures for data release of partially identifiable cancer data. Prevalent pancreatic cancer cases of patients aged 18 years or older residing within the state between January 1, 2010, and December 31, 2020, were included. Using the county the patient resided in at diagnosis, study participants were coded to one of the regions of North Carolina: mountain, piedmont, or coastal plains.

Water quality data was obtained from the National Water Quality Monitoring Council's (NWQMC) Water Quality Portal (WQP) for relevant water quality factors between January 1, 2000, and December 31, 2020. A total of 2,307,837 data points were obtained for 973 water quality factors. After review of the water quality data and current literature around the carcinogenic propensity of water quality factors, 15 variables were selected for inclusion in the study. Twenty-year means were calculated for each county in which the water quality factor was monitored. The mean value for each water quality factor was added to each patient record that resided in that county upon diagnosis. Given the non-parametric nature of the data, Kruskal-Wallis analyses were completed to examine the relationship between the research variables.

Limitations, Challenges, and Barriers

Water quality factors are not actively monitored in all 100 counties of North Carolina. As such, the regional averages for each water quality factor represents the average of only those counties within that region that monitor these factors. Additionally, it was noted that counties in the mountain region had a lower amount of water quality monitoring stations than those in the piedmont and coastal plains. As such, regional differences may be associated with the differential monitoring practices of the North Carolina Department of Environmental Quality. Furthermore, the cross-sectional study design provided a snapshot of the outcome of interest and the potential risk factors, allowing researchers to provide a description of the outcome of interest during the given timeframe (Levin, 2006). As such, the results of this study cannot provide temporal or causal associations between risk factors and the outcome of interest (Sedgwick, 2014).

Significance

The intent of these three studies is to contribute to the public health efforts to reduce the morbidity and mortality associated with pancreatic cancer in North Carolina. Due to the lack of conclusive evidence around risk factors for pancreatic cancer, the Unites States Preventative Services Task Force does not recommend screening for pancreatic cancer in the general population (Henrikson et al., 2019). Despite this, diagnosis with pancreatic cancer results in a 90% chance of death within 5 years. As such, the scientific community needs to continue to research societostrucutral and environmental risk factors for pancreatic cancer, growing the body of knowledge and identifying and developing screening procedures for high-risk individuals (familial risk, recent-onset diabetics, smoking, occupations that expose individuals to chemicals).

Additionally, despite the lack of evidence in this review, exposure to environmental contaminants poses as a significant risk factor for the development of cancer. Applying the previously described theories to pancreatic cancer risk provides the framework for researchers to connect exposures to adverse risk factors with neoplastic transformation of pancreatic cells. Excluding cases familial inheritance of pancreatic cancer, development of pancreatic cancer results from the accumulation of many genetic mutations that transform normal pancreas cells into toxic cancer cells. As such, one can envision how continued exposure to toxicity can manifest into the formation of cancer. Therefore, this necessitates the need for continued research into the environmental risks of pancreatic cancer.

Summary

Pancreatic cancer is one of the deadliest forms of cancer. Despite this, the scientific community lacks a general consensus as to the risk factors associated pancreatic cancer. To reduce the public health impact of pancreatic cancer, studies should continue to investigate the cause of regional variations in pancreatic cancer. While larger studies provide a summary of overall risk factors, these studies may mask small-scale associations. As such, smaller studies would provide more relevant information to those communities, allowing them to focus efforts to reducing the risk factors in their region. Lastly, as previously implied, additional modern research needs to focus on the association of environmental factors on pancreatic cancer. Specifically, more research around how air and water quality influence the manifestation of pancreatic cancer should be performed.

Part 2: Manuscripts

Quantitative Study Investigating the Association Between Societostructural/Medical Risk Factors and Pancreatic Cancer in North Carolina

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Design Plan Submitted in Partial Fulfillment

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Outlet for Manuscript

Cancer: This journal is a scholarly, peer-reviewed journal associated with the American Cancer Society that targets researchers and clinicians involved with cancer research. Primary research topics include risk reduction, detection, novel therapeutic treatments, and identifying and reducing health disparities in cancer. *Cancer*, one of the oldest oncology journals in the United States, publishes 24 issues per year in both print and online to a global audience. While subscriptions are required to access newer content, publications older than 12 months are open access through their online platform. *Cancer* accepts a variety of manuscripts including original articles, which report the findings of primary research.

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Abstract

With a 5-year survival rate of 10.3%, individuals diagnosed with pancreatic cancer face a life expectancy of 6 to 24 months. Despite ongoing research, detection of pancreatic cancer often occurs when the cancer is in the metastatic/terminal stage. As such, the best approach to reducing the morbidity and mortality associated with pancreatic cancer is to continue investigating risk factors. This study investigated the regional difference in pancreatic cancer risk factors in North Carolina. Data were obtained from the North Carolina Central Cancer Registry (NCCCR) and included adult pancreatic cancer patients whose diagnosis occurred while residing in North Carolina. Following a random selection of 1,200 study participants, pancreatic cancer patients in the mountain region were less likely to be Black (OR=.22) and have a history of diabetes (OR=.60). Pancreatic cancer patients in the piedmont region were less likely to be Native American/Alaskan (OR=.07) or have a smoking history (OR=.79) and more likely to have histories of pancreatic disorders (OR=1.33), biliary system disorders, (OR=2.26), esophageal disorders (OR=1.87), and show signs and symptoms (OR=2.27). Pancreatic cancer patients in the coastal plains region were less likely to have a history of biliary system disorders (OR=.52) and show signs and symptoms (OR=.57) and more likely to be Black (OR=1.87) or American Indian/Alaskan Native (OR=14.34) and have a smoking history (OR=1.41). The unique pattern of pancreatic cancer risk factors provides medical practitioners with the understanding of risk factors in their communities, providing them tools for the early identification of pancreatic cancer.

Introduction

In North Carolina, pancreatic cancer was the 10th most frequently occurring cancer and identified as one of the leading causes in cancer-related deaths among males and females for both the non-Hispanic white and non-Hispanic black ethnicities (State Center for Health Statistics, 2021). Furthermore, the incidence of pancreatic cancer has steadily risen 1.3% annually between 2002 and 2016 (NCI, 2021). Given this, identification of societostructural/medical risk factors, such as individual characteristics and lifestyle, is an optimal approach to reducing the mortality associated with pancreatic cancer.

Significance of This Study

Despite medical advances, pancreatic cancer remains a significant public health concern. The factors that contribute to the difficulty understanding pancreatic cancer are multifactorial. For example, pancreatic cancer often produces minimal, vague symptoms and is diagnosed in older individuals (McGuigan et al., 2018). As a result, pancreatic cancer is often diagnosed in later stages when the cancer has metastasized and treatment options are limited (Ilic & Ilic, 2016). Despite this, early detection of pancreatic cancer has yet to be solved, causing the U.S. Preventative Task Force to recommend against routine screening in asymptomatic adults (Henrikson et al., 2019). Furthermore, pancreatic cancer shows significant resistance to conventional chemotherapeutic and radiotherapeutic treatments (David et al., 2019).

Pancreatic cancer trends have been on the rise in North Carolina. The age-adjusted county-level incidence rate for pancreatic cancer in North Carolina between 2013 and 2017 ranged 22.0 to 9.1 cases per 100,000 (NCI, 2021). Consequently, mortality rates during this time frame ranged from 17.7 to 6.7 (NCI, 2021). As such, the most powerful tool to combat pancreatic cancer is to further investigate how societostructural/medical risk factors influence the development of pancreatic cancer.

Relevant Scholarship

An analysis of the relevent scholarship document that societostructural/medical risk factors associated with both individual characteristics and lifestyle are associated with pancreatic cancer (Cai et al., 2021; Khalaf et al., 2021; Maisonneuve, 2019). The societostructural factors investigated include age, gender, and race/ethnicity. The medical factors investigated include smoking history, comorbidities, and insurance status.

Societostructural Factors

Pancreatic cancer is most often diagnosed in individuals aged 75-74, with a median age at diagnosis of 70 (SEER, n.d.-a.). Between 2014 and 2018, approximately 10.8% of pancreatic cancer cases were diagnoses in individuals less than 54 years of age while 21.7%, 30.6%, 24.4%, and 12.9% of cases were diagnosed in ages 55-64, 65-74, 75-84, and 84 years and older, respectively (SEER, n.d.-a). Moreover, increased age was associated with increased risk and decreases survuvial of pancreatic cancer (Nipp et al., 2018; Siegel et al., 2019). Studies conducted by Andersson et al. (2016), Pang et al. (2017), and Wang et al. (2018) found slight increased odds of developing pancreatic cancer by gender. In these studies, increased odds were noted in females (Andersson et al, 2016; Wang et al., 2018), with increased odds for males noted in the study conducted by Pang et al..

Pancreatic cancer rates vary among race and ethnicities in the United States. In 2018, the incidence of pancreatic cancer per 100,000 individuals was 15.4, 13.3, 12.0, 10.1, and 9.9 in Black, White, Hispanic, Asian/Pacific Islander, and American Indian/Alaskan Native, respectively (SEER, n.d.-a). Nipp et al. (2018) found that early-stage pancreatic cancer survival rates were lower among Black (6.6. months), Hispanic (6.6 months), and Asian (6.7 months) when compared to White (9.0 months) patients. Furthermore, Black patients had higher incidences of late-stage pancreatic cancer and lower rates of early-stage pancreatic cancer when compared to White patients (Tavakkoli et al., 2020; Siegel et al., 2019).

Medical Factors

All studies that calculated risk estimates associated with smoking found significant increased risks of developing pancreatic cancer in their study populations. Specifically, risk estimates of developing pancreatic cancer ranged from 1.45 (Pang et al., 2018) to 11.83 (Hao et al., 2017) when compared to individuals who did not smoke. The second-most studied societostructural/medical risk factor studied was previous diagnosis with diabetes. As with smoking, all studies that calculated risk estimates associated with diabetes found significant increased risks of developing pancreatic cancer in their study populations (Zheng et al., 2019). Furthermore, the odds of developing pancreatic cancer were 1.72 and 1.98 when diabetes was diagnosed between 2-5 years and 5 years, respectively (Pang et al., 2017).

Recent studeies have investigated the association between pancreatic cancer and socioeconomic status. Chen et al., (2020) and Wong et al. (2017) found that regions with higher SDI, a measure of per capita income, educational attainment, and fertility rates, values had significantly higher levels of incidence and mortality associated with pancreatic cancer than regions with lower SDI values. Similarly, Huang et al. (2021) found that countries with very high human development indexes (HDI), a calculation that considers life expectancy, education level, and quality of life, were associated with increased rates of incidence and mortality to pancreatic cancer. Despite this, Siegel et al. (2019) found similar rates of pancreatic cancer mortality between 2012 and 2016 among poor and affluent patients (poor vs affluent rate ratio = 1.06).

Research Question and Design

This quantitative study investigated the association between societostructural/medical risk factors and pancreatic cancer in North Carolina.

Research Question

To what extent is there an association between regional levels of societostructural/medical risk factors and pancreatic cancer in North Carolina?

Null Hypothesis

There is not an association between regional levels of societostructural/medical risk factors and pancreatic cancer in North Carolina.

Alternate Hypothesis

There is an association between regional levels of societostructural/medical risk factors and pancreatic cancer in North Carolina.

Methods

Study Procedures

This study implemented a retrospective cross-sectional study design using a quantitative approach. A retrospective cross-sectional study design provides a snapshot of the outcome of interest and the potential risk factors, allowing researchers to provide a description of the outcome of interest during the given timeframe (Levin, 2006). Despite this, cross-sectional studies cannot provide temporal or causal associations between risk factors and the outcome of interest (Sedgwick, 2014). Given that this study is exploratory in nature, a cross-sectional study design is sufficient.

A data request was submitted and approved by the North Carolina Department of Health and Human Services, Division of Public Health, State Center for Health Statistics, Central Cancer Registry (DPH). All electronic data, including personally identifiable records, were stored on 256-bit AES keys that has been validated as being FIPS 140-2 certified. Study data was backed up using and Apricorn 500GB Aegis Padlock Fortress FIPS 140-2 level 2 validated 256-bit encrypted external hard drive with PIN access. There were no paper records associated with this study. Data obtained from the DPH for this study were defined as a limited data set as defined by 45 CFR §164.514(e). Personal health information (PHI) was not reused, disclosed, or transmitted to any other person or for research projects not approved under the fully executed data use agreement. The author of this study maintained sole access to the study data, maintaining confidentiality of study participant data. During the course of this study, the author did not experience any privacy/security incidents. Upon completion of the study, all electronic data were sterilized using NIST SP-800-88 data destruction standards.

Participants

Study participants for this study included North Carolina residents diagnosed with pancreatic cancer. Inclusion criteria included adult males and females above the age of 18 who's pancreatic cancer diagnosis occurred while residing in North Carolina between January 1, 2010, and December 31, 2020. Using data coding standards defined by SEER (n.d.-b.) and the American College of Surgeons (ACoS) (n.d.), patient records were filtered by ICD-O-2 or ICD-O-3 primary site codes associated with pancreatic cancer (Table 1) (SEER, n.d.-c.).

Table 1

Primary Site Codes: Pancreatic Cancer

ICD-O-2/3 Code	Primary site
C25.0	Head of pancreas
C25.1	Body of pancreas
C25.2	Tail of pancreas
C25.3	Pancreatic duct
C25.4	Islets of Langerhans
C25.7	Other specified parts of pancreas
C25.8	Overlapping lesion of pancreas
C25.9	Pancreas, NOS

Sample and Power

The rare nature of pancreatic cancer necessitates the accurate calculation of power and subsequent selection of study participants. Several factors were considered when determining the parameters of the power analysis. Specifically, the statewide incidence rate of pancreatic cancer between 2013 and 2017 was 13.1 cases per 100,000 individuals per year, with an average annual case count of 1,556 (NCI, 2020). Given the rare nature of pancreatic cancer, the power (β) was increased from the standard level of .8 to .95 (Miller et al., 2018). An *a priori* target sample size was calculated using G**Power* (Faul et al., 2007; Faul et al., 2009). A power analysis was completed using the following criteria: 1) two-tailed, 2) $\alpha = .05$, 3) Odds Ratio (effect size) = 1.3, and 4) $\beta = .95$, resulting in a proposed sample size of 1,188. Study participants were selected using a random sampling strategy.

Variables and Statistical Analysis

The pancreatic cancer obtained from the NCCCR contained 16,816 total study participant and included case-specific information about the patient's address/county at diagnosis, age at diagnosis, insurance information, primary cancer site, race, sex, diagnosis year, secondary diagnoses, and history of tobacco use. Duplicate entries were removed, resulting in a pool of 16,755 total potential study participants. Variables associated with insurance, primary cancer site, race, sex, and history of tobacco use were recoded into categorical variables.

Approximately 167,000 ICD-10 codes were evaluated and categorized into the following as bivariate categorical variables (no/yes):

- History of pancreas disorders – includes histories of pancreatitis (acute and chronic), pancreatic cysts, and pancreatic disorders identified in the patient record.
- Personal or familial history of all cancers – includes histories of any malignant neoplasm identified in the patient record.
- Personal or familial history of digestive cancers – includes histories of pancreatic, stomach, and colon cancer identified in the patient record.
- History of diabetes – includes histories of Type 1, Type 2 and prediabetes identified in the patient record.
- History of obesity – includes histories of obesity and high BMI identified in the patient record.
- History of liver disorders – includes histories of cirrhosis, hepatitis, hepatomegaly, and liver disorders identified in the patient record.
- History of biliary system disorders – includes histories of gall stones/disease and cholangitis/cholecystitis identified in the patient record.
- History of esophageal disorders – includes histories of esophageal disorders, esophageal varices, and gastroesophageal reflux (GERD) disease identified in the patient record.

- History of signs and symptoms – includes histories of abdominal pain, abdominal distension, blood in body samples, energy fluctuations (malaise and fatigue), enlarged lymph nodes, jaundice, nausea/vomiting, nutritional deficits, and weight fluctuations identified in the patient record.
- History of digestive system disorders – includes stomach disorders (gastris, pyloric stenosis, etc.), small intestinal disorders (duodenitis, intestinal blockages, etc.), large intestinal disorders (diverticulitis, ulcerative colitis, etc.), and overall digestive system disorders (Crohn's disease, gastrointestinal hemorrhage, etc.).

Information on other health-related disorders, such as cardiovascular disorders, cerebrovascular disorders, and musculoskeletal disorders, were present but not included in the scope of this study.

Using the county in which the sample was collected, data was then categorized into one of the three geographic regions of North Carolina. The regional designation for each study aligned with the major geographic regions of North Carolina: mountains, piedmont, and coastal plains (Figure 1). To investigate the relationship between the three regions, dummy bivariate categorical variables for the three regions were created:

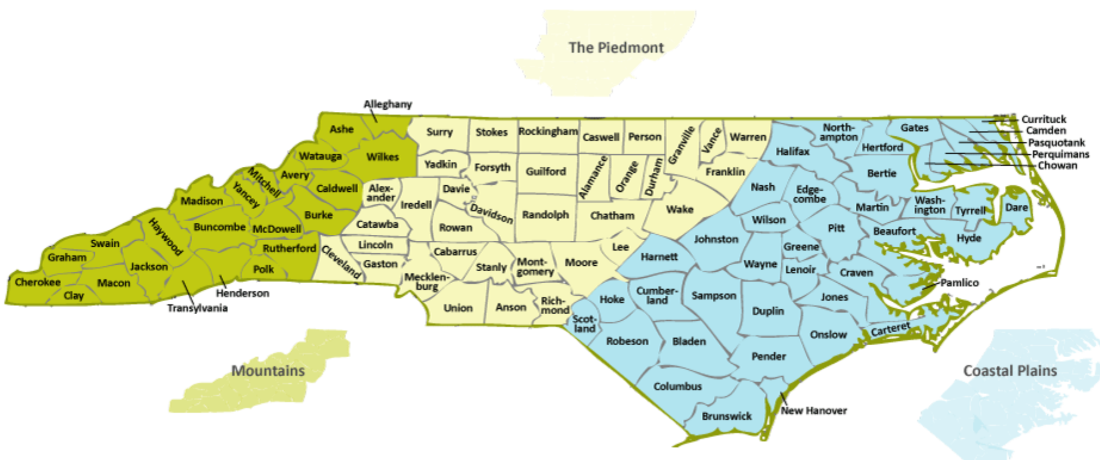
- Mountain – compared patients residing in the mountain region to those residing in the piedmont and coastal plains.
- Piedmont – compared patients residing in the piedmont region to those residing in the mountains and coastal plains.

- Coastal plains – compared patients residing in the coastal plain region to those residing in the piedmont and mountains.

The regionalization resulted in 23 counties residing in the mountain region, 36 counties residing in piedmont region, and 41 counties residing in the coastal plains region.

Figure 1

Major Geographic Regions of North Carolina



Note: Adapted from *Our State Geography in a Snap: Three Regions Overview*, by the North Carolina Department of Public Instruction, 2012 (https://www.dpi.nc.gov). In the public domain.

The data dictionary of all categorical variables included in this study can be found in Table 2.

Table 2

Data Dictionary for Variables Included in the Study

Variable name	Label	Level of measurement	Values	Missing
RGN	NC Region	Nominal	1=Mountains 2=Piedmont 3=Coastal Plains	None
AGE	Age at Diagnosis	Scale		None
INS	Insurance Status	Nominal	1=Not Insured 2=Private Insurance 3=Medicare/Medicaid 4=Military/Indian Services	98=Not known 99=No data
SITE	Primary cancer site	Nominal	1=Head of Pancreas 2=Body of Pancreas 3=Tail of Pancreas 4=Pancreatic Duct 5=Islets of Langerhans 6=Other specified Parts of Pancreas 7=Overlapping Lesions of Pancreas 8=Pancreas, not specific	None
RACE	Race	Nominal	1=White 2=Black 3=American Indian/Alaskan Native 4=Asian/Pacific Islander 5=Other	99= Unknown
SEX	Gender	Nominal	1=Male 2=Female 3=Other 4=Transsexual	99=Not State/ unknown
SMOKE	Smoking History	Nominal	0=Never Smoked 1=Smoking History	99= Unknown
HX_Pan	Pancreas Disorder History	Nominal	0=No 1=Yes	None
HX_ALL CA	Personal/ Family History of Cancer	Nominal	0=No 1=Yes	None
HX_DIG CA	Personal/ Family	Nominal	0=No 1=Yes	None

	History of Digestive Cancer			
HX_DIA	History of Diabetes	Nominal	0=No 1=Yes	None
HX_OBE	History of Obesity	Nominal	0=No 1=Yes	None
HX_LIV	History of Liver Disorder	Nominal	0=No 1=Yes	None
HX_BIL	History of Biliary System Disorder	Nominal	0=No 1=Yes	None
HX_ESO	History of Esophageal Disorder	Nominal	0=No 1=Yes	None
HS_SS	History of Signs and Symptoms	Nominal	0=No 1=Yes	None
HS_DIG	History of Digestive System Disorder	Nominal	0=No 1=Yes	None
MTN	Mountain Region	Nominal	0=Coastal Plains and Piedmont 1=Mountain	None
PIED	Piedmont Region	Nominal	0=Coastal Plains and Mountain 1=Piedmont	None
CSPL	Coastal Plains	Nominal	0=Mountains and Piedmont 1=Coastal Plains	None

Statistical Analysis

The pancreatic cancer patient data was loaded into the Statistical Package for the Social Sciences (SPSS) version 27 and a random selection of 1,200 study participants were selected. Descriptive statistics, including frequency distributions for all categorical variables as well as means for all continuous variables were generated to summarize the sample population. First, a series of Chi-square test of independence were performed to identify regional differences (RGN) and the following variables: INS, RACE, SEX, SMOKE, HX_PAN, HX_ALLCA, HX_DIGCA, HX_DIA, HX_OBE, HX_LIV, HX_BIL, HX_ESO, HX_SS, and HX_DIG. For the scale-level variable, AGE, a one-way ANOVA was conducted determine if there were any regional-level differences in the mean age of pancreatic cancer patients. To further investigate regional differences in the identified variables, a series of logistic regression models were performed. Specifically, bivariate nominal variables of MTN, PED, and CSTL were selected as dependent variables and entered into logistic regression models with independent variables that showed significant Chi-square associations. For all statistical tests, assumptions were assessed, measures of effect size were calculated, and the significance threshold was set at $\alpha = 0.05$.

Results

Descriptive Statistics

Of the 1,200 randomly selected study participants, 147 (12.3%) were from the mountain region, 680 (56.7%) were from the piedmont region, and 373 (31.1%) were from the coastal plains region. Most patients had carcinomas that resided in the head of the pancreas (45.9%) while the remaining patients had carcinomas originating in other regions of the pancreas. Approximately 73% of the study population were White (879), 23.6% (283) were Black, and the remaining 3.1% (38) were either Native

American/Alaskan Native, Asian/Pacific Islander, or other races. Males constituted 50.6% (607) while females constituted 49.4% (593) of the study population. Additionally, 67 (5.6%) had a history of pancreas disorders, 14 (1.2%) had a personal or family history of cancer, 2 (0.2%) had a personal or family history of digestive cancers, 134 (11.2%) had a history of diabetes, 28 (2.3%) had a history of obesity, 35 (2.9%) had a history of liver disorders, 53 (4.4%) had a history of biliary system disorders, 81 (6.8%) had a history of esophageal disorders, 155 (12.9%) had a history of signs and symptoms, and 42 (3.5%) had a history of digestive system disorders. A smoking history was found in 463 (56.0%) of the sample population and most study participants utilized Medicare/Medicaid (72.0%) as their primary insurance source. Descriptive statistics for all categorical study variables can be found in Table 3.

Table 3

Descriptive Statistics of Study Variables

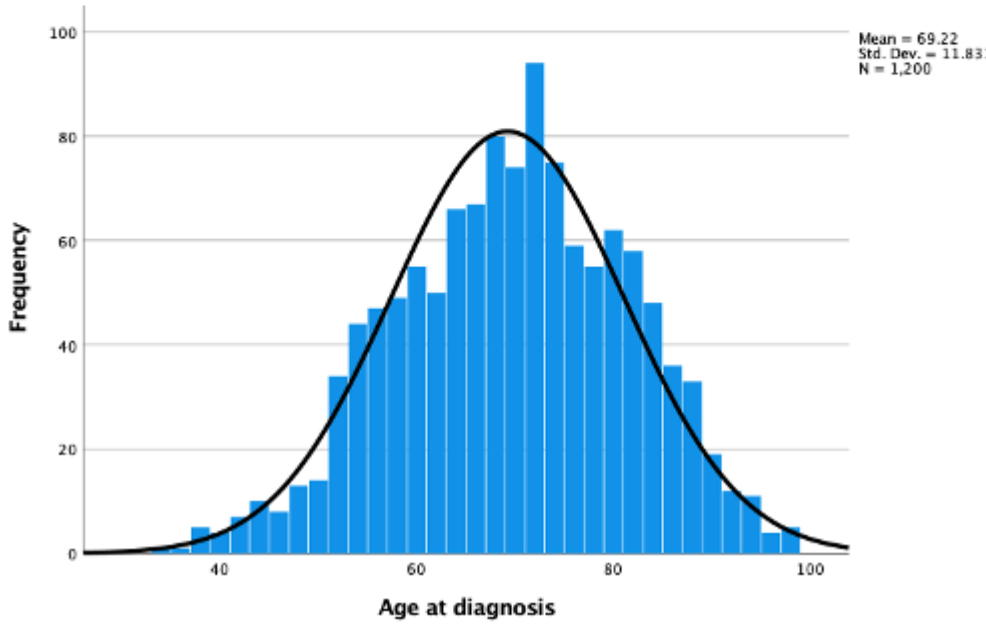
Variable	Values	Count	Percentage
Region	Mountains	147	12.3%
	Piedmont	680	56.7 %
	Coastal Plains	373	31.1%
Primary Cancer Site	Head of Pancreas	551	45.9%
	Body of Pancreas	157	13.1%
	Tail of Pancreas	192	16.0%
	Pancreatic Duct	4	0.3%
	Islets of Langerhans	1	0.1%
	Other specified Parts of Pancreas	28	2.3%
	Overlapping Lesions of Pancreas	72	6.0%
	Pancreas, not specific	195	16.3%
Race	White	879	73.3%
	Black	283	23.6%
	American Indian/Native Alaskan	12	1.0%
	Asian/Pacific Islander	16	1.3%

	Other	10	0.8%
Sex	Male	607	50.6%
	Female	593	49.4%
History of Pancreas Disorder	No	1,133	94.4%
	Yes	67	5.6%
Personal/Family History of Cancer	No	1,186	98.8%
	Yes	14	1.2%
Personal/Family History of Digestive Cancer	No	1,198	99.8%
	Yes	2	0.2%
History of Diabetes	No	1,066	88.8%
	Yes	134	11.2%
History of Obesity	No	1,172	97.7%
	Yes	28	2.3%
History of Liver Disorder	No	1,165	97.1%
	Yes	35	2.9%
History of Biliary System Disorder	No	1,147	95.6%
	Yes	53	4.4%
History of Esophageal Disorder	No	1,119	93.3%
	Yes	81	6.8%
History of Digestive System Disorder	No	1,158	96.5%
	Yes	42	3.5%
History of Signs and Symptoms	No	1,045	87.1%
	Yes	155	12.9%
History of Smoking	Never Smoked	364	44.0%
	Smoking History	463	56.0%
Insurance	Not Insured	23	4.0%
	Private Insurance	125	21.6%
	Medicare/Medicaid	416	72.0%
	Military/Indian Services	14	2.4%

The age of the study population ranged 18-99 years with a mean age of 69.23 (SD=12.23). A histogram distribution showed that the age variable was normally distributed (Figure 2).

Figure 2

Histogram Distribution of the Age Variable



Chi-Square Test of Independence/One-Way ANOVA

Results of the chi-square tests (Table 4) showed that insurance status, race, smoking history, history of pancreatic disorder, history of diabetes, history of biliary system disorder, history of esophageal disorders, history of signs and symptoms, and history of digestive system disorders were weakly associated with the North Carolina regions. Results associated with primary cancer site, gender, personal/family history of cancer, personal/family history of digestive cancer, history of obesity, and history of liver disorder did not identify significant associations to the North Carolina regions. It should be noted that due to small samples sizes for some values, the overall random sample size was increased to 5,000 randomly selected participants to ensure all tests had less than 20% expected cell counts less than five.

Table 4

Frequencies and Chi-Square Results for North Carolina Regions

Variable	Region: Mountains	Region: Piedmont	Coastal plains	X^2
Primary Cancer Site				22.76
Head of Pancreas	325 (49.5%)	1,294 (45.2%)	716 (48.5%)	
Body of Pancreas	105 (16.0%)	421 (14.7%)	173 (11.7%)	
Tail of Pancreas	93 (14.2%)	440 (15.4%)	232 (15.7%)	
Pancreatic Duct	1 (0.2%)	13 (0.5%)	7 (0.5%)	
Islets of Langerhans	0 (0.0%)	1 (0.0%)	2 (0.1%)	
Other specified Parts	9 (1.4%)	48 (1.7%)	18 (1.2%)	
Overlapping Regions	33 (5.0%)	176 (6.1%)	102 (6.9%)	
Pancreas, Not Specified	91 (13.9%)	473 (16.5%)	227 (15.4%)	
Insurance				21.77*
Not Insured	11 (3.2%)	42 (2.8%)	14 (2.0%)	
Private Insurance	70 (20.6%)	416 (28.2%)	148 (21.6%)	
Medicare/Medicaid	249 (73.2%)	974 (66.0%)	491 (71.6%)	
Military/Indian Services	10 (2.9%)	43 (2.9%)	33 (4.8)	
Race				228.62**
White	615 (93.8%)	2,121 (74.1%)	979 (66.3%)	
Black	34 (5.2%)	669 (23.4%)	457 (30.9%)	
American Indian/Alaskan	3 (0.5%)	8 (0.3%)	28 (1.9%)	
Asian/Pacific Islander	4 (0.6%)	37 (1.3%)	5 (0.3%)	
Other	0 (0.0%)	29 (1.0%)	8 (0.5%)	
Sex				6.71
Male	337 (52.7%)	1,328 (50.9%)	644 (49.5%)	
Female	278 (47.3%)	1,283 (49.1%)	656 (50.5%)	
Smoking History				19.39**
Never Smoked	210 (45.9%)	951 (45.3%)	379 (37.3%)	
Smoking History	248 (54.1%)	1,147 (54.7%)	636 (62.7%)	
Hx of Pancreas Disorder				14.41*
No	620 (94.4%)	2,651 (92.5%)	1,409 (95.4%)	
Yes	37 (5.6%)	215 (7.5%)	68 (4.6%)	
Hx Family/Personal Cancer				3.62
No	648 (98.6%)	2,816 (98.3%)	1,462 (99.0%)	
Yes	9 (1.4%)	50 (1.7%)	15 (1.0%)	
Hx Family/Personal Digestive Cancer				1.13
No	653 (99.4%)	2,850 (99.4%)	1,472 (99.7%)	
Yes	4 (0.6%)	16 (0.6%)	5 (0.3%)	
Hx Diabetes				10.51**
No	595 (90.6%)	2,459 (85.6%)	1,277 (86.1%)	
Yes	62 (9.4%)	407 (14.2%)	200 (13.5%)	

Hx Obesity					4.08
	No	643 (97.9%)	2,788 (97.3%)	1,451 (98.2%)	
	Yes	14 (2.1%)	78 (2.7%)	26 (1.8%)	
Hx Liver Disorder					4.53
	No	633 (96.3%)	2,760 (96.3%)	1,440 (97.5%)	
	Yes	24 (3.7%)	106 (3.7%)	37 (2.5%)	
Hx Biliary System Disorder					22.23**
	No	620 (94.4%)	2,706 (94.4%)	1,440 (97.5%)	
	Yes	37 (5.6%)	160 (5.6%)	37 (2.5%)	
Hx Esophageal Disorder					11.46*
	No	619 (94.2%)	2,626 (91.6%)	1,390 (94.2%)	
	Yes	38 (5.8%)	240 (8.4%)	87 (5.8%)	
Hx Signs/Symptoms					34.67**
	No	572 (87.1%)	2,459 (85.8%)	1,358 (91.9%)	
	Yes	85 (12.9%)	407 (14.2%)	119 (8.1%)	
Hx Digestive System Disorder	No	622 (94.7%)	2,705 (94.4%)	1,427 (96.6%)	10.65*
	Yes	35 (5.3%)	161 (5.6%)	50 (3.4%)	

Note: Parenthesis indicates percentage in each region. * $p < 0.05$. ** $p < 0.001$

A one-way ANOVA was conducted to determine if age was different among the regions of North Carolina. The Levene's test of homogeneity was not significant, indicating the variability was similar among all three regions. The age at diagnosis was not statistically significantly different among the three regions, $F(2,1197)=2.51$, $p=.081$.

Table 5

One-Way Analysis of Variance of Age among North Carolina Regions

	Mountains		Piedmont		Coastal Plains		*F*
Variable	N	M (SD)	N	M (SD)	N	M (SD)	(2,1197)
Age	147	71.29 (12.54)	680	68.8 (12.37)	373	69.2 (11.79)	2.51

Note: N represents sample size, M represents mean, SD represents standard deviation. * $p < 0.05$.

Logistic Regression Analyses

A series of simple binomial logistic regression was performed to ascertain the effects of independent variables who showed significant findings in the Chi-square and one-way ANOVA tests: insurance status, race, smoking history, history of pancreas disorders, history of diabetes, history of biliary system disorders, history of esophageal disorders, history of signs and symptoms, and history of digestive system disorders. Using bivariate categorical variables region variables (MTN, PIED, and CSTPL) as dependent variables, a series of simple logistic regression models were performed to determine associations to each independent variable separately. Lastly, all independent variables were then entered into multiple logistic regression models to analyze the complete association.

Mountain Region

Simple Logistic Regression. Pancreatic cancer patients in the mountain region showed a significant relationship with race, $X^2(4)=39.32$, $p < .001$, explaining 6.1% (Nagelkerke R^2) of the variability of the dependent variable. (Table 6). Specifically, Black pancreatic cancer patients were .18 ($p <.001$, 95% CI=.09 - .36) times less likely to live in the mountain region than other races.

Significant associations between insurance status, history of smoking, history of pancreatic disorder, history of diabetes, history of biliary system disorders, history of esophageal disorders, history of signs and symptoms, and history of digestive system disorders and living in the mountain region were not found. For all regression models, assumptions were tested and within established limits and the variables were determined to fit the model using the Hosmer and Lemeshow goodness of fit test.

Table 6

Simple Logistic Regression Results for the Mountain Region

Variable	*B* (SE)	*p*	Odds ratio (95% CI)
Insurance Status[a]			
Private Insurance	-.21 (.82)	.80	.82 (.16-4.04)
Medicare/Medicaid	.55 (.75)	.46	1.74 (.40-7.60)
Military/Indian Services	.66 (1.06)	.60	1.75 (.22-14.07)
Race[b]			
Black	-1.7 (.35)	<.001*	.18 (.09-.36)
American Indian/Alaskan Native	.11 (.78)	.89	1.12 (.24-5.13)
Asian	-.23 (.76)	.76	.79 (.18-3.54)
Other	-19.5 (12,710)	.99	-
History of Smoking[c]	-.02 (.22)	.93	.98 (.64-1.50)
History of Pancreatic Disorder[d]	-.37 (.44)	.40	.69 (.29-1.63)
History of Diabetes[e]	-.03 (.28)	.91	.97 (.56-1.68)
History of Biliary System Disorder[f]	-.31 (.48)	.52	.74 (.29-1.88)
History of Esophageal Disorder[g]	-.79 (.47)	.09	.45 (.18-1.14)
History of Signs/Symptoms[h]	-.14 (.27)	.60	.87 (.51-1.48)
History of Dig. System Disorders[i]	-.29 (.53)	.59	.75 (.26-2.13)

Note: Reference categories: [a] "Not Insured"; [b] "White"; [c] "No history of smoking"; [d] "No History of pancreatic disorder"; [e] "No history of diabetes"; [f] "No history of biliary system disorders"; [g] "No history of esophageal disorder"; [h] "No history of signs/symptoms"; [i] "No history of digestive system disorders". * indicates significant findings.

Multiple Logistic Regression. When all independent variables were added into a multiple logistic regression model the significance pattern associated with pancreatic cancer patients living in the mountain region changed slightly. The overall model was significant, $X^2(14)=31.09$, $p=.005$, explaining 11.1% (Nagelkerke R^2) of the variability of the dependent variable. Of the predictor variables investigated only two were statistically significant: race and history of diabetes (Table 8). Black pancreatic cancer patients were .22 (*p* =.002, 95% CI=.09–.57) times less likely to live in the mountain region while patients with a history of diabetes were .06 (*p*=.004, 95% CI= 43–.85) times less likely to live in the mountain region.

Significant associations between insurance status, history of smoking, history of pancreatic disorder, history of biliary system disorders, history of esophageal disorders, history of signs and symptoms, and history of digestive system disorders and living in the mountain region were not found. For all regression models, assumptions were tested and within established limits and the variables were determined to fit the model using the Hosmer and Lemeshow goodness of fit test.

Table 7

Multiple Logistic Regression Results for the Mountain Region

Variable	*B* (SE)	*p*	Odds ratio (95% CI)
Insurance Status[a]			
Private Insurance	-.88 (.88)	.32	.42 (.07-2.35)
Medicare/Medicaid	.16 (.79)	.84	1.17 (.25-5.52)
Military/Indian Services	.50 (1.11)	.65	1.65 (.19-14.51)
Race[b]			
Black	-1.52 (.49)	.002*	.22 (.09-.57)
American Indian/Alaskan Native	-19.4 (19,584)	.99	-
Asian	-1.23 (1.03)	.23	.29 (.04-2.21)
Other	-19.5 (17,747)	.99	-
History of Smoking[c]	-.01 (.29)	.98	.99 (.57-1.74)
History of Pancreatic Disorder[d]	-.98 (.63)	.12	.38 (.11-2.68)
History of Diabetes[e]	-.51 (.17)	.004*	.60 (.43-.85)
History of Biliary System Disorder[f]	-.48 (.54)	.37	1.62 (.56-4.66)
History of Esophageal Disorder[g]	-1.11 (.62)	.07	.33 (.1-1.11)

History of Signs/Symptoms[h]	-.18 (.37)	.63	.84 (.40-1.73)
History of Dig. System Disorders[i]	.09 (.59)	.88	1.1 (.35-3.45)

Note: Reference categories: [a] "Not Insured"; [b] "White"; [c] "No history of smoking"; [d] "No History of pancreatic disorder"; [e] "No history of diabetes"; [f] "No history of biliary system disorders"; [g] "No history of esophageal disorder"; [h] "No history of signs/symptoms"; [i] "No history of digestive system disorders". * indicates significant findings.

Piedmont Region

Simple Logistic Regression. Pancreatic cancer patients in the piedmont region showed a significant relationship with race, $X^2(4)=13.58$, $p=.009$, history of esophageal disorders, $X^2(1)=8.07$, $p=.004$, and signs and symptoms, $X^2(1)=8.07$, $p=.004$ (Table 8). American Indian/Alaskan Native pancreatic cancer patients were .07 ($p=.01$, 95% CI=.01-.55) times less likely to live in the piedmont region of North Carolina while those with a history of esophageal disorder and signs and symptoms were 1.78 ($p=.02$, 95% CI=1.09-2.89) and 1.66 ($p=0.005$, 95% CI=1.16-2.37) times more likely to live in the piedmont region, respectively.

Significant associations between insurance status, history of smoking, history of pancreatic disorder, history of diabetes, history of biliary system disorders, and history of digestive system disorders and living in the piedmont region were not found. For all regression models, assumptions were tested and within established limits and the variables were determined to fit the model using the Hosmer and Lemeshow goodness of fit test.

Table 8

Simple Logistic Regression Results for the Piedmont Region

Variable	*B* (SE)	*p*	Odds ratio (95% CI)
Insurance Status[a]			
Private Insurance	.16 (.48)	.74	1.18 (.46-3.00)
Medicare/Medicaid	-.47 (.45)	.30	.63 (.26-1.51)
Military/Indian Services	.29 (.74)	.70	1.33 (.32-5.64)
Race[b]			
Black	.11 (.14)	.45	1.12 (.85-1.46)
American Indian/Alaskan Native	-2.66 (1.05)	.01*	.07 (.01-.55)
Asian	.24 (.52)	.63	1.29 (.46-3.57)
Other	.15 (.65)	.82	1.16 (.33-4.13)
History of Smoking[c]	-.24 (.14)	.09	.78 (.60-1.04)
History of Pancreatic Disorder[d]	.33 (.26)	.20	1.40 (.84-2.33)
History of Diabetes[e]	.18 (.19)	.35	1.19 (.83-1.72)
History of Biliary System Disorder[f]	.60 (.31)	.05	1.81 (1.0-3.30)
History of Esophageal Disorder[g]	.58 (.25)	.02*	1.78 (1.09-2.89)
History of Signs/Symptoms[h]	.51 (.18)	.005*	1.66 (1.16-2.37)
History of Dig. System Disorders[i]	.33 (.33)	.31	1.39 (.73-2.65)

Note: Reference categories: [a] "Not Insured"; [b] "White"; [c] "No history of smoking"; [d] "No History of pancreatic disorder"; [e] "No history of diabetes"; [f] "No history of biliary system disorders"; [g] "No history of esophageal disorder"; [h] "No history of signs/symptoms"; [i] "No history of digestive system disorders". * indicates significant findings.

Multiple Logistic Regression. When all independent variables were added into a multiple logistic regression model the significance pattern associated with pancreatic cancer patients living in the piedmont region changed. The overall model was significant, $X^2(14)=44.89$, $p < .001$, explaining 10.6% (Nagelkerke R^2) of the variability of the dependent variable (Table 9). Of the predictor variables investigated six were statistically significant: race, history of esophageal disorders, and history of signs and symptoms retained significance while histories of smoking, pancreatic disorders, and biliary systems disorders also showed significance.

Pancreatic cancer patients of American Indian/Alaskan Native descent and those with a history of smoking were .07 (*p*=.01, 95% CI=.01–.55) and .79 (*p*=.006, 95% CI=.67–.93) times less likely to live in the piedmont region, respectively. Increased odds of living in the piedmont region were noted in patients with histories of esophageal disorders (*p*=.001, OR=1.87, 95% CI=1.01–3.44), signs and symptoms (*p*=.001, OR=2.27, 95% CI=1.42-3.65), pancreatic disorders (*p*=.04, OR=1.33, 95% CI=1.01–1.75), and biliary system disorders (*p*=.04, OR=2.26, 95% CI=1.03–4.96). Significant associations between insurance status, history of diabetes, and history of digestive system disorders and living in the piedmont region were not found. For all regression models, assumptions were tested and within established limits and the variables were determined to fit the model using the Hosmer and Lemeshow goodness of fit test.

Table 9

Multiple Logistic Regression Results for the Piedmont Region

Variable	*B* (SE)	*p*	Odds ratio (95% CI)
Insurance Status[a]			
Private Insurance	.48 (.51)	.35	1.61 (.60-4.38)
Medicare/Medicaid	-.18 (.46)	.70	.83 (.33-2.12)
Military/Indian Services	.57 (.76)	.45	1.77 (.40-7.79)
Race[b]			
Black	.11 (.14)	.45	1.12 (.85-1.46)
American Indian/Alaskan Native	-2.66 (1.05)	.01*	.07 (.01-.55)
Asian	.08 (.80)	.92	1.08 (.23-5.14)
Other	.10 (.10)	.92	1.10 (.17-7.14)
History of Smoking[c]	-.24 (.09)	.006*	.79 (.67-.93)

History of Pancreatic Disorder[d]	.29 (.14)	.04*	1.33 (1.01-1.75)
History of Diabetes[e]	-.03 (.23)	.90	.97 (.62-1.53)
History of Biliary System Disorder[f]	.82 (.40)	.04*	2.26 (1.03-4.96)
History of Esophageal Disorder[g]	.62 (.31)	.001*	1.87 (1.01-3.44)
History of Signs/Symptoms[h]	.82 (.24)	.001*	2.27 (1.42-3.65)
History of Dig. System Disorders[i]	.05 (.39)	.91	1.05 (.49-2.23)

Note: Reference categories: [a] "Not Insured"; [b] "White"; [c] "No history of smoking"; [d] "No History of pancreatic disorder"; [e] "No history of diabetes"; [f] "No history of biliary system disorders"; [g] "No history of esophageal disorder"; [h] "No history of signs/symptoms"; [i] "No history of digestive system disorders". * indicates significant findings.

Coastal Plains Region

Simple Logistic Regression. Pancreatic cancer patients in the coastal plains region showed a significant relationship with race, $X^2(4)=19.35$, *p*=.00, and history of signs and symptoms, $X^2(1)=7.35$, *p*=.007 (Table 10). Black pancreatic cancer patients were 1.54 (*p*=.003, 95% CI=1.16-2.04) and American Indian/Alaskan Native pancreatic cancer patients were 7.59 (*p*=.003, 95% CI=2.04-28.27) times more likely to live in the coastal plains region while those with histories of signs and symptoms were .59 (*p*=.009, 95% CI=.39-.88) times more likely to live in the coastal plains region.

Significant associations between insurance status, history of smoking, history of pancreatic disorder, history of diabetes, history of biliary system disorders, history of esophageal disorders, and history of digestive system disorders and living in the coastal plains region were not found. For all regression models, assumptions were tested and within established limits and the variables were determined to fit the model using the Hosmer and Lemeshow goodness of fit test.

Table 10

Simple Logistic Regression Results for the Coastal Plain Region

Variable	*B* (SE)	*p*	Odds ratio (95% CI)
Insurance Status[a]			
Private Insurance	-.11 (.52)	.83	.90 (.32-2.47)
Medicare/Medicaid	.28 (.49)	.57	1.32 (.51-3.42)
Military/Indian Services	-.75(.90)	.40	.47 (.08-2.75)
Race[b]			
Black	.43 (.14)	.003*	1.54 (1.16-2.04)
American Indian/Alaskan Native	2.03 (.67)	.003*	7.59 (2.04-28.3)
Asian	-.17 (.58)	.77	.84 (.30-2.64)
Other	.52 (.65)	.42	1.69 (.47-6.03)
History of Smoking[c]	.29 (.16)	.06	1.34 (1.0-1.81)
History of Pancreatic Disorder[d]	-.22 (.28)	.44	.81 (.46-1.40)
History of Diabetes[e]	-.19 (.21)	.36	.83 (.56-1.24)
History of Biliary System Disorder[f]	-.57 (.35)	.10	.57 (.29-1.12)
History of Esophageal Disorder[g]	-.34 (.27)	.20	.71 (.42-1.20)
History of Signs/Symptoms[h]	-.54 (.21)	.009*	.59 (.39-.88)
History of Dig. System Disorders[i]	-.25 (.36)	.49	.39 (.37-1.57)

Note: Reference categories: [a] “Not Insured”; [b] “White”; [c] “No history of smoking”; [d] “No History of pancreatic disorder”; [e] “No history of diabetes”; [f] “No history of biliary system disorders”; [g] “No history of esophageal disorder”; [h] “No history of signs/symptoms”; [i] “No history of digestive system disorders”. * indicates significant findings.

Multiple Logistic Regression. When all independent variables were added into a multiple logistic regression model the significance pattern associated with pancreatic cancer patients living in the coastal plains region changed (Table 11). The overall model was significant, $X^2(14)=45.61$, $p<.001$, explaining 11.4% (Nagelkerke R^2) of the variability of the dependent variable. Of the predictor variables investigated four were statistically significant: race and history of signs and symptoms retained significance while histories of smoking and biliary system disorders also showed significance.

Pancreatic cancer patients with histories of biliary system disorders and signs and symptoms were .52 (*p*=.002, 95% CI=.34–.78) and .57 (*p*<.001, 95% CI=.44-.74) times less likely to live in the coastal plains region. Pancreatic cancer patients of Black and American Indian/Alaskan Native descent were 1.87 (*p*<.001, 95% CI=1.51–2.30) and 14.34 (*p*<.001, 95% CI=3.8–53.7) times more likely to live in the coastal plains while those with smoking histories were 1.41 (*p*=.001, 95% CI=1.16–1.70) times more likely to live in the coastal plains.

Significant associations between insurance status, history of pancreatic disorder, history of diabetes, history of esophageal disorders, and history of digestive system disorders and living in the coastal plains region were not found. For all regression models, assumptions were tested and within established limits and the variables were determined to fit the model using the Hosmer and Lemeshow goodness of fit test.

Table 11

Multiple Logistic Regression Results for the Coastal Plain Region

Variable	*B* (SE)	*p*	Odds ratio (95% CI)
Insurance Status[a]			
Private Insurance	-.25 (.55)	.65	.78 (.26-2.28)
Medicare/Medicaid	.11 (.52)	.83	1.12 (.41-3.07)
Military/Indian Services	-1.10 (.92)	.24	.34 (.06-2.04)
Race[b]			
Black	.62 (.11)	<.001*	1.87 (1.51-2.30)
American Indian/Alaskan Native	22.66 (.67)	<.001*	14.34 (3.8-53.7)
Asian	.64 (.80)	.42	1.90 (.40-9.03)

Other	.63 (.96)	.52	1.87 (.28-12.34)
History of Smoking[c]	.34 (.10)	.001*	1.41 (1.16-1.70)
History of Pancreatic Disorder[d]	.33 (.35)	.34	1.40 (.71-2.77)
History of Diabetes[e]	-.13 (.25)	.62	.88 (.54-1.44)
History of Biliary System Disorder[f]	-.66 (.21)	.002*	.52 (.34-.78)
History of Esophageal Disorder[g]	-.30 (.34)	.38	.74 (.39-1.44)
History of Signs/Symptoms[h]	-.56 (.13)	.<001*	.57 (.44-.74)
History of Dig. System Disorders[i]	-.14 (.44)	.74	.87 (.37-2.05)

Note: Reference categories: [a] "Not Insured"; [b] "White"; [c] "No history of smoking"; [d] "No History of pancreatic disorder"; [e] "No history of diabetes"; [f] "No history of biliary system disorders"; [g] "No history of esophageal disorder"; [h] "No history of signs/symptoms"; [i] "No history of digestive system disorders". * indicates significant findings.

Discussion

The results of this study support the idea that the patten of societostructural/medical risk factors varies among the different regions of North Carolina. Specifically, the Chi-square analyses showed significant weak differences in insurance status, race, smoking history, history of pancreatic disorders, history of diabetes, history of biliary system disorder, history of esophageal disorders, history of signs and symptoms, and history of digestive system disorders among pancreatic cancer patients living in the mountain, piedmont, and coastal plains regions of North Carolina. The subsequent logistic regression analyses of these risk factors identified unique risks of these societostructural/medical risk factors in each region, providing evidence to reject the null hypothesis and conclude that regional variations in societostructural/medical risk factors exist in North Carolina pancreatic cancer patients.

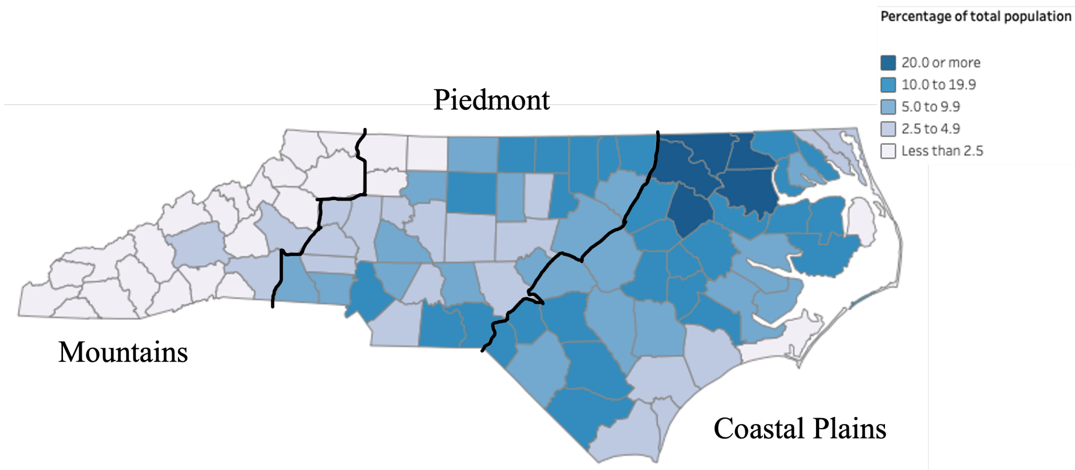
Sociodemographic Factors

Race/Ethnicity

Results of the Chi-square and logistic regression analyses support the conclusion that there are regional differences in the racial/ethnic distribution of pancreatic cancer patients in North Carolina. Black pancreatic cancer patients were less likely to live in the mountain region and more likely to live in the coastal plains region. Furthermore, American Indian/Alaskan Native pancreatic cancer patients were less likely to live in the piedmont region and more likely to live in the coastal plains region. These findings are supported by other studies (Chen et al., 2020; Klein, 2021), but should be considered with caution. The methodological nature of this study was not to identify racial/ethnic risk of developing pancreatic cancer in each region, but to identify regional racial/ethnic differences in the incidence of pancreatic cancer. A more probable conclusion is that this finding may be associated with the distribution of the Black and American Indian/Alaskan Native populations throughout North Carolina and is not unique to the pancreatic cancer population. According to the United States Census Bureau (2021), counties in the mountain region have lower percentages while counties in the coastal plains region have a high percentage of the Black population in North Carolina (Figure 3).

Figure 3

Black/African American Population in North Carolina

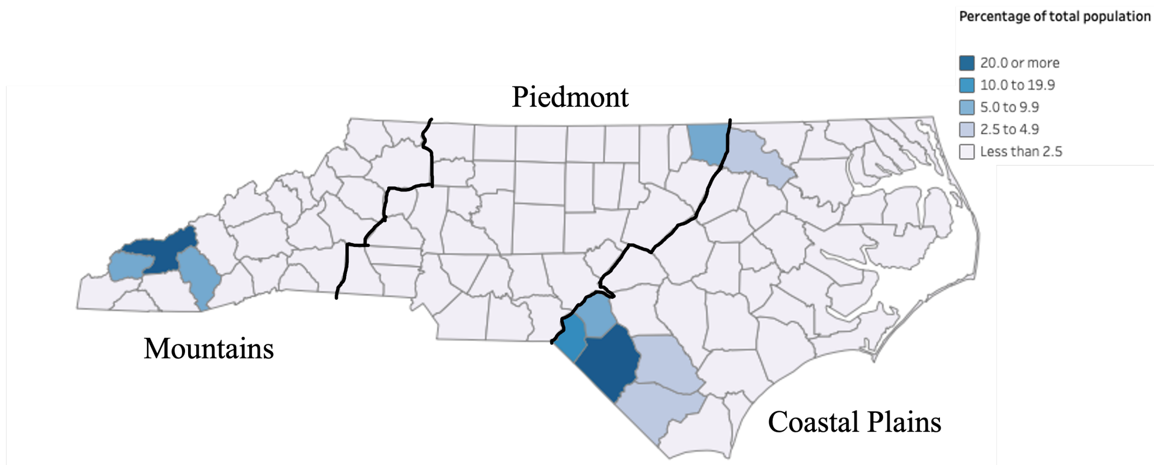


Note: Adapted from *North Carolina: 2020 Census*, by the United States Census Bureau, 20021 (https://www.census.gov). In the public domain.

Similarly, the American Indian/Alaskan Native population is more concentrated in the mountain and coastal plains regions of North Carolina (United States Census Bureau, 2021) (Figure 4), aligning with the geographic location of state and federally recognized Indian tribes (North Carolina Department of Administration, Commission of Indian Affairs, n.d.). It is noted that despite the large population of individuals from the Eastern Band of Cherokee Indians in the mountain region, the incidence of American Indians/Alaskan Native's with pancreatic cancer was lowest (0.5%) when compared to other regions. Further investigation is needed to identify the disparity in this observation.

Figure 3

American Indian/Alaskan Native Population in North Carolina



Note: Adapted from *North Carolina: 2020 Census*, by the United States Census Bureau, 20021 (https://www.census.gov). In the public domain.

Medical Factors

History of Smoking

Pancreatic cancer patients with a history of smoking were .79 times less likely to live in the piedmont region and 1.41 times more likely to live in the coastal plains region of North Carolina. These findings align with previous studies showing individual who smoke have an increased risk of developing pancreatic cancer (Huang et al., 2019; Pang et al., 2018). However, North Carolina has a rich agricultural history in tobacco farming. According to the United States Department of Agriculture (2021), five counties in the piedmont and 12 counties in the coastal plains are the largest producers of tobacco in North Carolina. As such, the association between smoking and living in the coastal plains region may be associated with cultural and economic history of tobacco farming rather than an increased risk of developing pancreatic cancer.

Medical Disorders

In 2021, 12.4% of the North Carolina population have a diabetes diagnosis (American Diabetes Association, 2021). This study found that pancreatic cancer patients with a history of diabetes were .60 times less likely to live in the mountain region. Furthermore, the mountain region had the lowest incidence of pancreatic cancer in North Carolina. Studies by Pothuraju at al. (2018) show that diabetes contributes to the development of pancreatic cancer by altering metabolic pathways associated with the function of the pancreas. As such, it is probable that the decreased likelihood of pancreatic cancer patients with a diabetic history residing in the mountain region contributes to the lower incidence of pancreatic cancer in this region.

Similarly, clinical manifestations of gastrointestinal disorders, such as pancreatic disorders and biliary system disorders alter pancreatic function and may contribute to the neoplastic transformation of pancreatic cancer (Huang et al., 2020; Kikuyama et. al., 2018). Furthermore, proton-pump inhibitors, commonly prescribed to treat esophageal reflux disorders, may result in an increased risk of pancreatic cancer (Peng et al., 2018). The results of this study showed that pancreatic cancer patients with a history of pancreatic, biliary system, and esophageal disorders were 1.33, 2.26, and 1.87 times, respectively, more likely to live in the piedmont region. Consequently, this study also found that the piedmont region had the highest incidence of pancreatic cancer in North Carolina. One interpretation of these results is that the increased likelihood of pancreatic cancer patients with a history of pancreas disorders contributes to the higher incidence of pancreatic cancer in this region. However, it is noted that these disorders can be caused by both inherited and lifestyle factors, such as diet and alcohol consumption. As such, this study is not able to ascertain the scope of influence inherited and lifestyle factors has on these diseases in the piedmont region.

Lastly, pancreatic cancer is characterized by the late onset of symptoms (Gheorge et al., 2020), presenting challenges detecting the presence of pancreatic cancer (Henrikson et al., 2019). As such, early detection of pancreatic cancer relies on the identification of both risk factors and signs and symptoms, such as jaundice, weight loss, and vitamin/nutrition deficiencies (U.S. Preventive Services Task Force, 2019). This study found that pancreatic cancer patients who showed signs and symptoms were 2.27 times more likely to live in the piedmont region. Furthermore, pancreatic cancer patients in the piedmont region showed increased significant associations to four of the nine independent variables. In comparison, pancreatic cancer patients in the coastal plains region, which has the second highest incidence of pancreatic cancer, showed increased significant associations to two of the nine independent variables while those in the mountain region, which had the lowest incidence of pancreatic cancer, did not show increased significant associations to study variables. As such, this study supports previous research findings that the accumulation of risk factors may contribute to the manifestation of pancreatic cancer.

Limitations

The cross-sectional nature of this study provides limitations to the interpretation and use of the study information. Specifically, temporal or causal associations cannot be inferred from this study. Secondly, the study is limited by the interpretation and ICD-10 coding practices of clinical professionals treating pancreatic cancer patients. The use of relevant secondary diagnosis codes in this study was contingent on the interpretation of clinical presentation and the subsequent assigning of the relevant ICD-10 code to the pancreatic patient's medical record. It is plausible that some clinical professionals could apply incorrect ICD-10 codes or fail to apply a relevant ICD-10 code. Additionally, the nature of the cancer registry information makes it impossible to identify the timepoint in which the code was applies. As such, it is impossible to identify if the ICD-10 code was applied before or after the manifestation of pancreatic cancer. Lastly, this study only investigated the presence of risk factors in North Carolina. It is likely that the regional differences observed are the result of regional variations in exposures to carcinogenic agents, such as toxins in air and water quality. However, such investigation is beyond the scope of this study and is a recommendation for future studies.

Conclusion

Pancreatic cancer is one of the most aggressive forms of cancer and is associated with a poor prognosis for survival. Despite continued efforts to understand the etiology of pancreatic cancer, little remains known about effective identification and preventative measures. Results of this study showed regional differences in societostructural/medical risk factors for pancreatic cancer in North Carolina. The pattern of accumulation of risk factors was unique to each region, likely contributing to the overall incidence of that region. Additionally, the unique pattern of risk factors in each region contributes to the foundation of knowledge about pancreatic cancer risk factors and allows healthcare providers to understand how those risk factors may contribute to the pancreatic cancer patients in their region. As such, North Carolina healthcare providers can contextualize their approach to identifying patients at risk of pancreatic cancer earlier, promoting social change and reducing the overall mortality and morbidity of pancreatic cancer.

The findings and conclusion in this publication are those of the author(s) and does not necessarily represent the views of the North Carolina Department of Health and Human Services, Division of Public Health.

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Quantitative Study Investigating the Association Between Air Quality and Pancreatic Cancer in North Carolina

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Abstract

Pancreatic cancer produces minimal symptoms and is known as one of the deadliest cancers. Despite ongoing research, detection of pancreatic cancer often occurs when the cancer is in the metastatic/terminal stage. As such, the best approach to reducing the morbidity and mortality associated with pancreatic cancer is to continue investigating risk factors. This study investigated the regional difference in relevant air quality factors among North Carolina pancreatic cancer patients. Cancer data were obtained from the North Carolina Central Cancer Registry (NCCCR) and included a 10-year history of adult pancreatic cancer patients whose diagnosis occurred while residing in North Carolina. Air quality data were obtained from the Environmental Protection Agency (EPA) and included a 20-year history of 11 air quality factors. Following a random selection of 1,200 study participants, Kruskal-Wallis results showed that there was statistically significant differential long-term exposure of air quality factors among pancreatic cancer patients in the mountain, piedmont, and coastal plains region. The piedmont region, which showed the highest incidence of pancreatic cancer, was found to contain 45.5% (5/11) of highest levels: air quality index (AQI), ozone (O_3), sulfur dioxide (SO_2), fine particulate matter ($PM_{2.5}$), and nitric oxide (NO). Patterns of pancreatic cancer incidence matched the pattern of significantly different $PM_{2.5}$ levels across the three regions. Given the carcinogenic nature of $PM_{2.5}$, future research is needed to further identify potential associations. Understanding the air quality factors present in each region provides

medical practitioners with the understanding of potential pancreatic cancer risk factors in their communities.

Introduction

Air pollution poses a significant risk to human health. In 1970, the Environmental Protection Agency established the Clean Air Act, establishing National Ambient Air Quality Standards (NAAQS) to regulate emissions and protect public health from six common pollutants in outdoor air (Environmental Protection Agency [EPA], 2020). Under the auspices of this Act, the NAAQS identifies carbon monoxide (CO), lead (Pb), nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2), and two forms of particulate air matter ($PM_{2.5}$ and PM_{10}) as six criteria air pollutants. These pollutants contaminate the air by forming complex mixtures of small particles, gases, and liquid droplets (World Health Organization [WHO], 2021b).

Sources of air pollution are associated with natural and anthropogenic sources, such as emission from vehicles, burning of fuels oil and natural gas, smoke from wildfire, ae well as by-products from industrial and coal-burning power production (National Institute of Environmental Health Sciences [NIEHS], 2021). In 2013, the World Health Organization's (WHO) International Agency for Research on Cancer (IARC; 2013) classified air pollution as a carcinogenic, stating that exposure to air pollution causes inflammation and oxidative stress at the cellular level, establishing the platform for chronic disease and neoplastic transformation of cells.

Significance of This Study

Despite medical advances, pancreatic cancer remains a significant public health concern. The factors that contribute to the difficulty understanding pancreatic cancer are multifactorial. For example, pancreatic cancer often produces minimal, vague symptoms and is diagnosed in older individuals (McGuigan et al., 2018). As a result, pancreatic cancer is often diagnosed in later stages when the cancer has metastasized and treatment options are limited (Ilic & Ilic, 2016). Despite this, early detection of pancreatic cancer has yet to be solved, causing the U.S. Preventative Task Force to recommend against routine screening in asymptomatic adults (Henrikson et al., 2019). Furthermore, pancreatic cancer shows significant resistance to conventional chemotherapeutic and radiotherapeutic treatments (David et al., 2019).

In North Carolina, pancreatic cancer trends have risen. Specifically, the age-adjusted county-level incidence rate for pancreatic cancer in North Carolina between 2013 and 2017 ranged 22.0 to 9.1 cases per 100,000 (NCI, 2021). Consequently, mortality rates during this time frame ranged from 17.7 to 6.7 (NCI, 2020). Additionally, the NCDEQ reports that significant improvements in air quality have been made in response to the Clean Air Act. Since 1990, state-wide levels of SO_2, CO, nitrogen oxides (NO_x), $PM_{2.5}$, and volatile organic compounds (VOCs) have decreased 91%, 69%, 63%, 49%, and 60%, respectively (NCDEQ, 2020). Despite these significant improvements in air quality, studies show that cancer-related manifestations to air quality are associated with long term exposure (Kim et al., 2018). As such, one way to understand the manifestation of pancreatic cancer is to further investigate how long-term air quality exposure influences the development of pancreatic cancer.

Relevant Scholarship

An analysis of the relevent scholarship document that air-quality factors are associated with the manifestation of cancer. Emerging environmental health studies show a combination of abhorrent lifestyle factors, genetic susceptibility, and long-term exposure to air pollutants are associated with significant risk of cancer (Cazzolla Gatti, 2021; Kim et al., 2018). Specifically, cancer incidence was significantly associated with poor air quality originating from industrial, farming, and transportation sources.

Industrial Sources of Air Pollution

North Carolina is home to many potential forms of industrial air pollution. For example, North Carolina is home to the largest electric power company, furniture manufacturing companies, and textile mill industry in the Unites States (North Carolina Department of Commerce, n.d.). Furthermore, North Carolina houses the second-largest food processing and manufacturing companies, third-largest U.S. financial center, and fifth-largest plastics and chemicals workforce (North Carolina Department of Commerce, n.d.). Lastly, the abundance of research-based universities attracts biotech and pharm companies such as Merck and GlaxoSmithKline to the Research Triangle Park in North Carolina (North Carolina Department of Commerce, n.d.).

Exposure to sources of industrial-based air pollution is associated with the incidence of many forms of cancer. Cong (2018) found that air pollution from industrial gas was significantly positively associated with incidences of multiple forms of cancer. In a geospatial analysis, Vigotti et al. (2014) found higher cancer-related mortality values were associated with industrial areas, spreading to surrounding neighborhoods. Additionally, Baum et al. (2020) found that when controlling for age, individuals living in urban regions were 1.3 times more likely to develop pancreatic cancer than those living in rural areas.

Farming Sources of Air Pollution

North Carolina's history is rich in agriculture. Specifically, North Carolina is home to more than 52,000 farms covering 8.4 million acres, which is 27% of the land in North Carolina (North Carolina Department of Agriculture & Consumer Services [NCDACS], n.d.). Of these farms, 1,600 farms are consider century farms, meaning they have been in operation for more than 100 years (NCDACS, n.d.). North Carolina produces more than 150 agricultural products (NCDACS, n.d.). Hogs, chickens, and turkeys are the largest sources of livestock while tobacco and sweet potatoes are the largest source of crops in North Carolina (NCDACS, n.d.). In 2019, North Carolina generated approximately $10.6 billion associated with the production and processing of agricultural products, equating to 5.1% of the total Gross Domestic Product (GDP) of the state (NCDACS, n.d.).

By-products of the agricultural industry, such as pesticides and animal waste, can be aeresolized, posing a cancer risk (Beene Freeman, 2012; Lee et al., 2012). Associations between direct and indirect exposure to aerosolized agricultural pesiticides and pancreatic cancer were somewhat inconclusive. Studies conducted by Antwi et al. (2015), and Kachuri et al. (2017) found significant risk estimates associated with pancreatic cancer and direct exposure (OR=1.21 and HR=1.36, respectively) while Louis et al. (2017) found significant risk estimates associated with pancreatic cancer and indirect exposure to lindane (OR=3.7) but failed to find significant associations between pancreatic cancer and DDT and chlordane in female spouses of pesticide applicators. However, Fritschi et al. (2015) did not find significant associations between pancreatic cancer and exposures to pesticides or *N*–nitrosamines.

Transportation Sources of Air Pollution

North Carolina is home to 107, 348 miles of road, 3,161 miles or railroads, and is home to 14 airports (U.S. Department of Transportation [USDOT], 2020). As of 2017, North Carolina had 8.5 million registered vehicles (USDOT, 2020). Of the 10.5 million individual living in North Carolina, 80.6% drive an average of 36.4 miles a day to work alone (USDOT, 2020). In 2018, North Carolina saw 121.1 billion of vehicle miles traveled (USDOT, 2020). Additionally, in 2018 North Carolina saw 31.2 million enplanements (USDOT, 2020).

The burning of fossil fuels associated with transportation results in the emission of carbon-based and greenhouse gasses, such as methane, nitrous oxide, and hydrofluorocarbons, into the atmosphere (EPA, n.d.). Communities near heavily trafficked areas have higher levels of greenhouse gasses (Ragettli et al., 2015). Additionally, Heck et al. (2013) found weak associations between exposure to trafficbased air pollution and rare childhood cancers. Furthermore, Cohen et al. (2018) found that after a mean exposure of 7.0 years to traffic-related air pollution, cardiac patients had an increased risk of cancer formation. Kim et al. (2018) found that PM_{10} levels were significantly associated with pancreatic cancer mortality. Lastly, Wang et al. (2018) found that $PM_{2.5}$ air pollition was significantly, slightly associated with increased risk of pancreatic cancer, increasing with age and urbanicity.

Research Question and Design

This quantitative study investigated the association between air quality and pancreatic cancer in North Carolina.

Research Question

To what extent is there an association between regional air quality levels and pancreatic cancer in North Carolina?

Null Hypothesis

There is not an association between regional air quality levels and pancreatic cancer in North Carolina.

Alternate Hypothesis

There is an association between regional air quality levels and pancreatic cancer in North Carolina.

Methods

Study Procedures

This study implemented a retrospective cross-sectional study design using a quantitative approach. A retrospective cross-sectional study design provides a snapshot of the outcome of interest and the potential risk factors, allowing researchers to provide a description of the outcome of interest during the given timeframe (Levin, 2006). Despite this, cross-sectional studies cannot provide temporal or causal associations between risk factors and the outcome of interest (Sedgwick, 2014). Given that this study is exploratory in nature, a cross-sectional study design is sufficient.

A data request was submitted and approved by the North Carolina Department of Health and Human Services, Division of Public Health, State Center for Health Statistics, Central Cancer Registry (DPH). All electronic data, including personally identifiable records, were stored on 256-bit AES keys that has been validated as being FIPS 140-2 certified. Study data was backed up using and Apricorn 500GB Aegis Padlock Fortress FIPS 140-2 level 2 validated 256-bit encrypted external hard drive with PIN access. There were no paper records associated with this study. Data obtained from the DPH for this study were defined as a limited data set as defined by 45 CFR §164.514(e). Personal health information (PHI) was not reused, disclosed, or transmitted to any other person or for research projects not approved under the fully executed data use agreement. The author of this study maintained sole access to the study data, maintaining confidentiality of study participant data. During this study, the author did not experience any privacy/security incidents. Upon completion of the study, all electronic data were sterilized using NIST SP-800-88 data destruction standards.

Participants

Study participants for this study included North Carolina residents diagnosed with pancreatic cancer. Inclusion criteria includes adult males and females above the age of 18 who's pancreatic cancer diagnosis occurred while residing in North Carolina between January 1, 2010, and December 31, 2020. Using data coding standards defined by SEER (n.d.-b.) and the American College of Surgeons (ACoS) (n.d.), patient records were filtered by ICD-O-2 or ICD-O-3 primary site codes associated with pancreatic cancer (Table 1) (SEER, n.d.-c.).

Table 1

Primary Site Codes: Pancreatic Cancer

ICD-O-2/3 Code	Primary site
C250	Head of pancreas
C251	Body of pancreas
C252	Tail of pancreas
C253	Pancreatic duct
C254	Islets of Langerhans
C257	Other specified parts of pancreas
C258	Overlapping lesion of pancreas
C259	Pancreas, NOS

Sample and Power

The rare nature of pancreatic cancer necessitates the accurate calculation of power and subsequent selection of study participants. Several factors were considered when determining the parameters of the power analysis. Specifically, the statewide incidence rate of pancreatic cancer between 2013 and 2017 was 13.1 cases per 100,000 individuals per year, with an average annual case count of 1,556 (NCI, 2020). Given the rare nature of pancreatic cancer, the power (β) was increased from the standard level of .8 to .95 (Miller et al., 2018). An *a priori* target sample size was calculated using G**Power* (Faul et al., 2007; Faul et al., 2009). A power analysis was completed using the following criteria: 1) two-tailed, 2) $\alpha = .05$, 3) Odds Ratio (effect size) = 1.3, and 4) $\beta = .95$, resulting in a proposed sample size of 1,188. Study participants were selected using a random sampling strategy.

Variables and Statistical Analysis

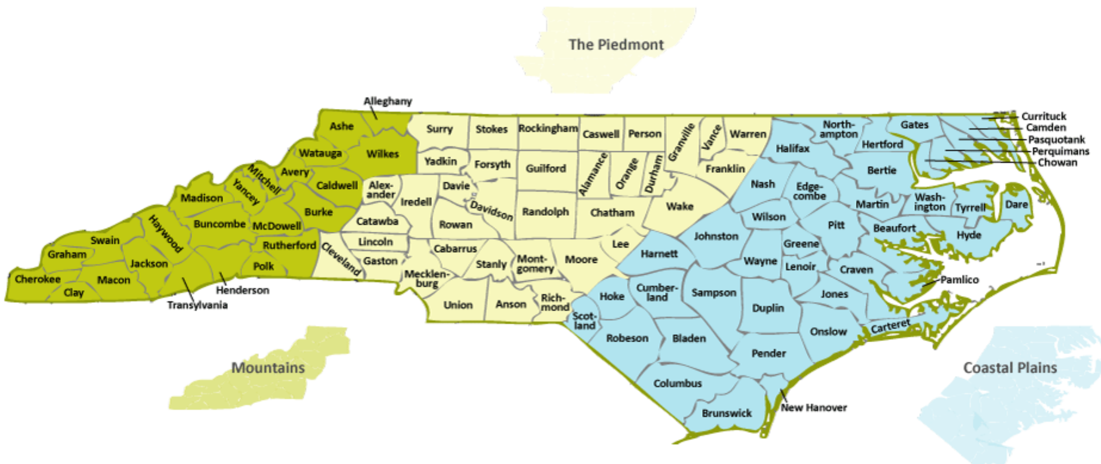
Cancer-Related Data

The pancreatic cancer obtained from the NCCCR contained 16,816 total study participant and included case-specific information about the patient's address/county at diagnosis, age at diagnosis, insurance information, primary cancer site, race, sex, diagnosis year, secondary diagnoses, and history of tobacco use. Duplicate entries were removed, resulting in a pool of 16,756 total potential study participants.

Using the county the patient resided in at diagnosis, study participants were coded to one of the regions of North Carolina: Mountain, Piedmont, or Coastal Plains. The regionalization resulted in 23 counties residing in the mountain region, 36 counties residing in piedmont region, and 41 counties residing in the coastal plains region. The data dictionary of all nominal variables included in this study can be found in Table 2.

Figure 1

Major Geographic Regions of North Carolina



Note: Adapted from *Our State Geography in a Snap: Three Regions Overview*, by the North Carolina Department of Public Instruction, 2012 (https://www.dpi.nc.gov). In the public domain.

Table 2

Data Dictionary for Nominal Variables Included in the Study

Variable name	Label	Level of measurement	Values	Missing
RGN	NC Region	Nominal	1=Mountains 2=Piedmont 3=Coastal Plains	None

Air Quality Data

Air quality data was obtained from the Environmental Protection Agency (EPA) for relevant air quality factors between January 1, 2000, and December 31, 2020. Air quality data obtained from the EPA were filtered to isolate North Carolina-specific data and included measures of:

1. Air quality indices (AQI)–248,220 results obtained.
2. Criteria gases (ozone [O_3], sulfur dioxide [SO_2], carbon monoxide [CO], and nitrogen dioxide [NO_2])–449,753 results obtained.
3. Particulate matter ($PM_{2.5}$ & PM^{10})–256,947 results obtained.
4. Toxics, precursors, and lead (hazardous air pollutants [HAPs], hydrocarbon/volatile organic compounds [VOCs], nitrogen oxides [NO, NO_x, NO_Y], and lead [Pb])–698,422 results obtained for 115 factors.

The data files obtained included relevant information, including parameter name, sampling strategies and durations, dates the samples were collected, daily arithmetic means, daily maximum values, and the county in which the sample was collected.

After review of the air quality data and current literature around the carcinogenic propensity of air quality factors, the following variables were selected for inclusion in the study:

- Air Quality Index (AQI)
- Criteria gas: Carbon monoxide (CO), Nitrogen dioxide (NO_2), Ozone (O_3), Sulfur dioxide (SO_2)
- Particulate Matter: Particulate Matter 2.5 ($PM_{2.5}$), Particulate Matter 10 (PM_{10})
- Toxics, precursors, and lead: Hazardous air pollutant: Benzene, Volatile organic compound: Ethylbenzene, Nitric Oxide (NO), Lead (Pb-$PM_{2.5}$)

Air quality variable data were combined with the pancreatic cancer database. It should be noted that air quality factors are not actively monitored in all 100 North

Carolina counties. Twenty-year means were calculated for each county in which the air quality factor was monitored. The mean value for each air quality factor was added to each patient record that resided in that county upon diagnosis. For example, if a patient resided in Cumberland County at diagnosis, then the 20-year average for AQI for Cumberland County was entered for their AQI value in the database. When county-specific data were not available, a 20-year mean was calculated using data from the surrounding counties. For example, CO values were not recorded for Caldwell County. Therefore, CO values for contiguous counties of Alexander, Catawba, Burke, Avery, Watauga, and Wilkes were used estimate the CO value for Caldwell County. This resulted in each pancreatic cancer patient having the relevant 20-year average value as the data point for each air quality factor monitored in the county they resided in upon diagnosis.

Statistical Analysis

The pancreatic cancer patient data was loaded into the Statistical Package for the Social Sciences (SPSS) version 27 and a random selection of 1,200 study participants were selected to accommodate for the low number of air quality sampling measures. Descriptive statistics, including frequency distributions for all categorical variables as well as measure of central tendency for all continuous variables were generated to summarize the sample population. Since the air quality data was determined to be nonparametric, a series of Kurskal-Wallis was used to determine differences in median air quality values among the different regions of North Carolina. Since the Kruskal-

Wallis test only identifies the presence of a significant difference among the three regional groups, post hoc analysis using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons was performed to identify exact significant differences between the regions. For all statistical tests, assumptions were assessed, measures of effect size were calculated, and the significance threshold was set at $\alpha = 0.05$.

Results

Descriptive Statistics

Of the 1,200 randomly selected study participants, 147 (12.3%) were from the mountain region, 680 (56.7%) were from the piedmont region, and 373 (31.1%) were from the coastal plains region. The descriptive statistics for scale-level air quality variables include mean, median, minimum, maximum, count, and standard deviation (Table 3).

Table 3

Descriptive Statistics for Air Quality Variables

Air quality factor (level of measurement)	Mean	Median	Std. Deviation	Minimum	Maximum
AQI	47.03	47.18	6.98	18.04	56.90
CO (ppm)	0.59	0.49	0.44	0.33	5.29
NO_2 (ppb)	7.63	7.23	2.94	0.002	11.06
O_3 (ppm)	0.033	0.033	0.003	0.003	0.046
SO_2 (ppb)	1.57	1.52	0.93	0.003	4.25
$PM_{2.5}$ (µg/m^3)	10.48	10.77	1.28	6.83	14.91
PM_{10} (µg/m^3)	16.68	16.66	3.20	0.027	27.30
Benzene (ppb)	1.45	1.31	0.37	0.50	2.28
Ethylbenzene (ppb)	0.53	0.53	0.11	0.011	0.68
NO (ppb)	2.70	2.75	1.67	0.04	5.29

Pb-$PM_{2.5}$ (μg/m^3)	0.002	0.002	0.001	0.000	0.004

Kruskal-Wallis Test

Results of the Kruskal-Wallis tests found significant differences in at least one North Carolina region for all air quality factors investigated (Table 4). Distributions of air quality values were similar, as assessed by visual inspection of a boxplot. To isolate exact median differences among the North Carolina regions, pairwise comparisons were performed in a post hoc analysis.

AQI

Median AQI values were statistically significantly different among the regions of North Carolina. Median AQI values in the piedmont (*Mdn*=52.57) were significantly higher than the mountain (*Mdn*=43.03, adjusted p<.001) and coastal plains (*Mdn* =43.23, adjusted p<.001) regions.

Criteria Gases

Median values for all criteria gases (CO, NO_2, O_3, and SO_2) were statistically significantly different between the three regions of North Carolina. Post hoc analysis showed that the mountain region contained significantly (adjusted p<.001) higher median levels of NO_2 (*Mdn*=10.97 ppb) than the piedmont (*Mdn*=9.70 ppb) and coastal plains (*Mdn*=5.97 ppb) regions. The piedmont region contained significantly (adjusted p<.001) higher median levels of O_3 (*Mdn*=.0335 ppm) and SO_2 (*Mdn*=1.552 ppb) than the mountain (*Mdn*=.0329 ppm and *Mdn*=1.05 ppb, respectively) and coastal plains (*Mdn*=.0326 ppm and *Mdn*=1.28 ppb, respectively) regions. Lastly, the coastal plains region had significantly (adjusted p<.001) higher median levels of CO (*Mdn*=.6341 ppm) than the piedmont (*Mdn*=.4289 ppm) and mountain (*Mdn*=.4008 ppm) regions.

Particulate Matter

Median values for all particulate matter ($PM_{2.5}$ and PM_{10}) were statistically significantly different between the three regions of North Carolina. Post hoc analysis showed that the mountain region contained significantly (adjusted p<.001) higher median levels of PM_{10} (*Mdn*=18.37 μg/m^3) than the piedmont (*Mdn*=16.66 μg/m^3) and coastal plains (*Mdn*=15.63 μg/m^3) regions while the Piedmont contained significantly (adjusted p<.001) higher median levels of $PM_{2.5}$ (*Mdn*=10.88 μg/m^3) than the mountain (*Mdn*=9.50 μg/m^3) and coastal plains (*Mdn*=9.78 μg/m^3) regions.

Toxics, Precursors, and Lead

Median values for all toxics, precursors, and lead (benzene, ethylbenzene, NO, and Pb-$PM_{2.5}$) were statistically significantly different between the three regions of North Carolina. Post hoc analysis showed that the mountain region contained significantly (adjusted p<.001) higher median levels of benzene (*Mdn*=2.28 ppb) and ethylbenzene (*Mdn*=.6344 ppb) than the piedmont (*Mdn*=1.31 ppm and *Mdn*=.5269 ppb, respectively) and coastal plains (*Mdn*=1.26 ppm and *Mdn*=.4921 ppb, respectively) regions. The piedmont region contained significantly (adjusted p<.001) higher median levels of NO (*Mdn*=4.22 ppb) than the mountain (*Mdn*=1.21 ppb) and coastal plains (*Mdn*=1.22 ppb) regions. Lastly, the coastal plains region had significantly (adjusted p<.001) higher median levels of Pb-$PM_{2.5}$ (*Mdn*=.0022 μg/m^3) than the piedmont (*Mdn*=.0020 μg/m^3) and mountain (*Mdn*=.0012 μg/m^3) regions.

Table 4

Kruskal-Wallis Results of Air Quality Among the North Carolina Regions

Air quality factor (level of measurement)	X^2	Median		
		Mountain	Piedmont	Coastal Plains
AQI	649.74**	43.03^{b}	52.57^{ac}	43.23^{b}
CO (ppm)	400.81**	0.4008^{bc}	0.4286^{ac}	0.6341^{ab}
NO_2 (ppb)	468.33**	10.97^{bc}	9.70^{ac}	5.97^{ab}
O_3 (ppm)	150.57**	0.0329^{b}	0.0335^{ac}	0.0326^{b}
SO_2 (ppb)	45.07**	1.05^{ac}	1.52^{a}	1.28^{a}
$PM_{2.5}$ (μg/m^3)	374.38**	9.50^{bc}	10.88^{ac}	9.78^{ab}
PM_{10} (μg/m^3)	118.39**	18.37^{bc}	16.66^{ac}	15.63^{ab}
Benzene (ppb)	462.97**	2.28^{bc}	1.31^{ac}	1.26^{ab}
Ethylbenzene (ppb)	319.84**	0.6344^{bc}	0.5269^{ac}	0.4921^{ab}
NO (ppb)	499.18**	1.21^{b}	4.22a^{c}	1.22^{b}
Pb-$PM_{2.5}$ (μg/m^3)	141.30**	0.0012^{bc}	0.0020^{a}	0.0022^{a}

Note: Statistically significant differences between other regions are designated by the following: ^{a}mountain, ^{b}piedmont, ^{c}coastal plains; $^{*}p<.05$, $^{**}p<.001$

Discussion

Results of this study showed significant differences between relevant air quality factors among the three regions of North Carolina. Specifically, the mountain region was noted in having the highest levels of NO_2, PM_{10}, benzene, and ethylbenzene. The piedmont region was noted for having the highest levels of AQI, O_3, SO_2, $PM_{2.5}$, and NO while the coastal plain region was noted for having the highest levels of CO and Pb-$PM_{2.5}$. Furthermore, it was noted that the piedmont region contained 45.5% (5/11) of the highest levels of air quality factors, followed by the mountain region (36.4% or 4/11) and the coastal plains region (18.2% or 2/12). As such, there is a significant difference among the 20-year history of air quality factors in North Carolina pancreatic cancer patients.

Regional variations in relevant air quality factors are associated with differences in weather patterns (i.e., temperature, wind, and climate change), geographic features (i.e., mountain ranges and coastlines), and human activity (fossil fuel combustion and industrial emissions) (National Center for Atmospheric Research [NCAR], n.d.). However, certain insight can be gained by comparing the pattern of air quality differences with the incidence of pancreatic cancer among North Carolina regions. Specifically, the piedmont region showed the highest incidence of pancreatic cancer, followed by the coastal plains and mountain region, respectively. In the piedmont region, AQI, O_3, SO_2, $PM_{2.5}$, and NO showed a similar pattern of differences. While significant differences were noted among at least two of the three regions for AQI, O_3, SO_2, and NO in North Carolina pancreatic cancer patients, $PM_{2.5}$ was found to both align with the pattern of pancreatic cancer incidence and be significantly different among all three regions.

These results align with previous studies investigating the association between $PM_{2.5}$ and digestive cancers, including pancreatic cancer. Coleman et al. (2017) found increased hazard ratio associated with $PM_{2.5}$ and both stomach (HR=1.87, 95% CI=1.202.92, *n*=525) and colorectal (HR=1.29, 95% CI=1.05-1.58, *n*=2,572) cancers. These findings are supported by Wong et al. (2016), who found increased hazard ratios associated with both upper digestive tract (HR=1.42, 95% CI=1.06-1.89, *n*=323) and accessory organ (HR=1.35, 95% CI=1.06-1.71, *n*=676) cancers. Furthermore, Bogumi et al. (2021) found an increased hazard ratio associated with incident pancreatic cancer (HR=1.61, 95% CI=1.60-8.06, *n*=821), with an average follow-up time of 16 years.

Studies investigating the carcinogenic biological mechanisms of $PM_{2.5}$ support the potential of pancreatic cancer etiology. Indirect models show that $PM_{2.5}$ exposure contributes to the epigenetic silencing of tumor suppressor genes such as *TP53*, which is involved in the cellular monitoring of cell proliferation, apoptosis, and DNA damage repair (Zhou et al, 2016). $PM_{2.5}$ has also been shown to modify cancer-related signaling pathways through hypomethylation, transcriptional activation of oncogenic genes and microRNAs (Heßelbach et al., 2017), facilitating neoplastic transformation of cells. As such, it is plausible that the carinogenic biological actions of $PM_{2.5}$ may contribute to the initiation, promotion, and progression of pancreatic cancer in a time-dependent multi-step carcinogenic process (Turner et al., 2020).

Limitations

One of the biggest limitations to this study is the availability of county-level air quality data. Specifically, air quality factors are sparsely measured throughout North Carolina, making county-level associations difficult to investigate. For example, the monitoring of criteria gasses, benzene, and ethylbenzene were largely missing in the mountain region of North Carolina. While appropriate adjustments were made to calculate the potential levels of these factors during the 20-year history investigated, it is plausible that these adjustments do not reflect accurate levels of these factors in this region. Additionally, the cross-sectional nature of this study provides limitations to the interpretation and use of the study information. As such, temporal or causal associations cannot be inferred from this study. Lastly, this study only investigated the association between regional air quality differences and the pancreatic cancer incidence in North Carolina. It is likely that the regional differences observed are also affected by covariables such as race, the presence of specific risk factors to pancreatic cancer, and smoking history. However, due to the nature of the data available, such investigation is beyond the scope of this study and is a recommendation for future studies.

Conclusion

Pancreatic cancer is one of the most aggressive forms of cancer and is associated with a poor prognosis for survival. Despite continued efforts to understand the etiology of pancreatic cancer, little remains known about the long-term environmental factors that place individuals at risk for developing pancreatic cancer. Results of this study showed significant, regional differences in relevant air quality factors in pancreatic cancer patients residing in North Carolina. While the pattern of AQI, SO_2, and NO levels mirrored the pattern of pancreatic cancer incidence in North Carolina, $PM_{2.5}$ was the only air quality factor investigated that both mirrored the pattern of pancreatic cancer incidence and showed statistically significant differences among all three regions. Given the carcinogenic nature of $PM_{2,5}$, it is plausible that long-term exposure could play a role in the incidence of pancreatic cancer in each region. Additionally, the historical presence of carcinogenic air pollutants in each region contributes to the foundation of knowledge about potential pancreatic cancer risk factors, allowing healthcare providers to understand how those risk factors may contribute to the pancreatic cancer patients in their region. As such, North Carolina healthcare providers can contextualize their approach to identifying patients at risk of pancreatic cancer earlier, promoting social change and reducing the overall mortality and morbidity of pancreatic cancer.

The findings and conclusion in this publication are those of the author(s) and does not necessarily represent the views of the North Carolina Department of Health and Human Services, Division of Public Health.

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Quantitative Study Investigating the Association Between Water Quality and Pancreatic Cancer in North Carolina

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Abstract

Pancreatic cancer produces minimal symptoms and is known as one of the deadliest cancers. Despite ongoing research, detection of pancreatic cancer often occurs when the cancer is in the metastatic/terminal stage. As such, the best approach to reducing the morbidity and mortality associated with pancreatic cancer is to continue investigating risk factors. This study investigated the regional difference in relevant water quality factors among North Carolina pancreatic cancer patients. Cancer data were obtained from the North Carolina Central Cancer Registry (NCCCR) and included a 10-year history of adult pancreatic cancer patients whose diagnosis occurred while residing in North Carolina. Water quality data were obtained from the Water Quality Exchange (WQX) and included a 20-year history of 15 water quality factors. Following a random selection of 1,200 study participants, Kruskal-Wallis results showed that there was statistically significant differential long-term exposure of water quality factors among pancreatic cancer patients in the mountain, piedmont, and coastal plains region. The piedmont region, which showed the highest incidence of pancreatic cancer, was found to contain the highest levels of cadmium and nitrogen, which have been associated with pancreatic cancer in other studies. The piedmont also contained the highest levels of chromium, lead, and metolachlor, known carcinogens. Given the carcinogenic nature of these factors, future research is needed to further identify potential associations. Understanding the water quality factors present in each region provides medical practitioners with the understanding of potential pancreatic cancer risk factors in their communities.

Introduction

Water contaminated by biological, chemical, and radiological sources is a significant public health concern. The chemical and physical characteristics of water allows molecules to become attracted to other molecules, giving water the ability to dissolve more substances than any other liquid (United States Geological Society [USGS], 2021). As such, toxic substances from organic pollutants, petroleum, heavy metals, pesticides, fertilizers, radionucleotides, pharmaceutical by-products, microplastics, and human and animal waste readily dissolve in water sources, causing an accumulation of toxins and poisons (EPA, 2021b). Since communities use water sources for drinking, food preparation, and recreation, the accumulation of toxic substances renders such sources unsafe for use (WHO, 2021a).

In 1948, the EPA established the Federal Water Pollution Control Act (later renamed the Clean Water Act) to address growing water pollution concerns (EPA, 2021b). The Clean Water Act established standards for toxic water conditions, regulations for discharging pollutants into water sources, and afforded the EPA with the authority to implement pollution control programs (EPA, 2021b). Such standards include regulations for all water sources (ground, surface, and ocean) as well as point (contamination from a single source), nonpoint (contamination from a diffuse source) and transboundary (pollution that crosses established boundaries) sources (National Resources Defense Council [NRDC], 2021). State agencies, such as NCDEQ, are legally obligated to adhere, monitor, and report data associated with the EPA standards (NCDEQ, 2021).

Water pollution stems from anthropogenic sources, such as industrial sites, agricultural sources, and sewage/septic systems (Levallois & Villanueva, 2019). Exposure to toxins from these sources causes deficiencies in cell-specific detoxification pathways and oxidative stress, inducing DNA damage and establishing the platform for chronic disease and neoplastic transformation of cells in mammals (Baines et al., 2021). Therefore, the investigation of water pollution is a justifiable approach to understanding the etiology of pancreatic cancer.

Significance of This Study

Despite medical advances, pancreatic cancer remains a significant public health concern. The factors that contribute to the difficulty understanding pancreatic cancer are multifactorial. For example, pancreatic cancer often produces minimal, vague symptoms and is diagnosed in older individuals (McGuigan et al., 2018). As a result, pancreatic cancer is often diagnosed in later stages when the cancer has metastasized and treatment options are limited (Ilic & Ilic, 2016). Despite this, early detection of pancreatic cancer has yet to be solved, causing the U.S. Preventative Task Force to recommend against routine screening in asymptomatic adults (Henrikson et al., 2019). Furthermore, pancreatic cancer shows significant resistance to conventional chemotherapeutic and radiotherapeutic treatments (David et al., 2019).

In North Carolina, pancreatic cancer trends have risen. Specifically, the age-adjusted county-level incidence rate for pancreatic cancer in North Carolina between 2013 and 2017 ranged 22.0 to 9.1 cases per 100,000 (NCI, 2020). Consequently, mortality rates during this time frame ranged from 17.7 to 6.7 (NCI, 2020). During this time, North Carolina has also documented instances of both point and nonpoint contamination of drinking and recreational water sources. According to the National Institute of Environmental Health, North Carolina ranks third in the United States for per- and polyfluoroalkyl substances (PFAS) exposure (Scruggs, 2019). North Carolina ground water sources have also been shown to have historical contamination of industrial-based carcinogens such as arsenic (Evans et al., 2019; Sanders et al., 2012), 1,4-dioxane (NCDEQ, n.d.-a.), and trihalomethanes (Hood, 2005). Lastly, North Carolina's rich history in agriculture has contributed to known accumulations of fecal coliform (NCDEQ, 2019) and chlorinated hydrocarbons (USGS, 2015).

North Carolina's 17 river basins serve as a primary source for drinking water and recreation (NCDEQ, n.d.-c.), providing hydrological connections between its citizens. As water flows across the state towards the Atlantic Ocean, there is the potential for the accumulation of toxins. Specifically, contamination events that occur upstream can accumulate and combine with other point sources of emission, resulting in deleterious effects on individuals living downstream. Studies show that cancer-related manifestations are associated with long term exposure to environmental contaminants (Baines et al., 2021). As such, one way to understand the manifestation of pancreatic cancer is to further investigate how long-term exposure to contaminated water sources influences the development of pancreatic cancer.

Relevant Scholarship

An analysis of the relevent scholarship document that water-quality factors are associated with the manifestation of cancer. Emerging environmental health studies show a combination of abhorrent lifestyle factors, genetic susceptibility, and long-term exposure to water pollutants are associated with significant risk of cancer (Baines et al., 2021). However, North Carolina has relevant history of point and nonpoint sources of contamination that have released carcinogenic toxins into drinking and recreational water sources.

In February 2014, a broken pipe leaked 39,000 tons of coal ash from the nearby Duke Energy Dan River Steam Station into the Dan River, extending more than 70 miles downriver (EPA, 2014). Coal ash, a by-product of generating power from coal, resulted in the accumulation of carbon and various heavy metals such as arsenic, lead, mercury, and zinc into the Dan River, which serves as a recreational waterway as well as a drinking water source for many communities in North Carolina and Virginia (EPA, 2014). According to the EPA (2007), individuals living near coal ash have a 1 in 50 chance of developing cancer. Additionally, the U.S. Commission on Civil Rights (2016) found that racial minorities and low-income communities are disproportionately affected by sources of water pollution such as coal ash. As such, the disproportionate exposure of coal ash to racial minorities and low-income communities throughout the Dan River watershed may contribute to the disparities in pancreatic cancer among African Americans in North Carolina (Tavakkoli et al., 2020).

In June 2017, the NCDEQ began an investigation into the accumulation of GenX, a synthetic organoflourine chemical compound used in the manufacturing of per- and polyfluoroalkyl substance (PFAS) such as Teflon, in the Cape Fear River basin, which serves as a drinking water source for more than 1.6 million North Carolinians (NCDEQ, n.d.-b.). Results of the investigation showed that Chemours, a Du-Pont company, was found to have been releasing the chemical into the Cape Fear River basin since 1980 (NCDEQ, n.d.-b.). Studies by Duke University show that GenX byproducts were found in 75% of the blood samples tested and the chemical was still present in the water 5 months after the leakage was stopped (Kotlarz et al., 2019). GenX has been shown to have negative health effects on the liver, kidney, and immune system (EPA, 2021c) and is considered a carcinogen of the liver, pancreas, and testicles (North Carolina Department of Health and Human Services [NCDHHS], 2017). At this time, exposure to GenX is only thought to occur through contamination of ground and surface water sources (Herkert et al., 2020), indicating that the Chemours leak was the likely source of the GenX exposure in North Carolina.

North Carolina is home to more than 52,000 farms covering 8.4 million acres, which is 27% of the land in North Carolina (NCDACS, n.d.). North Carolina is also subject to adverse weather event such as hurricanes, causing extensive flooding capable of contaminating public and private water sources. During Hurricane Florence in

September 2018, eastern North Carolina saw more than 30 inches of rainfall, resulting in extensive flooding and causing agricultural waste to leak into many watersheds (NCDEQ, 2019). Temporal analysis showed accumulations of polycyclic aromatic hydrocarbons (PAHs), elevated levels of fecal coliform, depletion of dissolved oxygen levels, and increases in nitrate, volatile organics, and heavy metals (NCDEQ, 2019). Of these, PAHs (Aly et al., 2021), NO_x (International Agency for Research on Cancer [IRAC], 2010), VOCs (Williams et al., 2002), and heavy metals including mercury, lead, chromium, cadmium, and arsenic (Balali-Mood et al., 2021; Kim et al., 2015) have been shown to cause various forms of cancer, including digestive-based cancers. As such, continued flooding of eastern North Carolina following hurricanes may place individuals at a higher risk of developing cancer, including pancreatic cancer.

Research Question and Design

This quantitative study investigated the association between water quality and pancreatic cancer in North Carolina.

Research Question

To what extent is there an association between regional water quality levels and pancreatic cancer in North Carolina?

Null Hypothesis

There is not an association between regional water quality levels and pancreatic cancer in North Carolina.

Alternate Hypothesis

There is an association between regional water quality levels and pancreatic cancer in North Carolina.

Methods

Study Procedures

This study implemented a retrospective cross-sectional study design using a quantitative approach. A retrospective cross-sectional study design provides a snapshot of the outcome of interest and the potential risk factors, allowing researchers to provide a description of the outcome of interest during the given timeframe (Levin, 2006). Despite this, cross-sectional studies cannot provide temporal or causal associations between risk factors and the outcome of interest (Sedgwick, 2014). Given that this study is exploratory in nature, a cross-sectional study design is sufficient.

A data request was submitted and approved by the North Carolina Department of Health and Human Services, Division of Public Health, State Center for Health Statistics, Central Cancer Registry (DPH). All electronic data, including personally identifiable records, were stored on 256-bit AES keys that has been validated as being FIPS 140-2 certified. Study data was backed up using and Apricorn 500GB Aegis Padlock Fortress FIPS 140-2 level 2 validated 256-bit encrypted external hard drive with PIN access. There were no paper records associated with this study. Data obtained from the DPH for this study were defined as a limited data set as defined by 45 CFR §164.514(e). Personal health information (PHI) was not reused, disclosed, or transmitted to any other person or for research projects not approved under the fully executed data use agreement. The author of this study maintained sole access to the study data, maintaining confidentiality of study participant data. During the course of this study, the author did not experience any privacy/security incidents. Upon completion of the study, all electronic data were sterilized using NIST SP-800-88 data destruction standards.

Participants

Study participants for this study include North Carolina residents diagnosed with pancreatic cancer. Inclusion criteria includes adult males and females above the age of 18 who's pancreatic cancer diagnosis occurred while residing in North Carolina between January 1, 2010, and December 31, 2020. Using data coding standards defined by SEER (n.d.-b.) and the American College of Surgeons (ACoS) (n.d.), patient records will be filtered by ICD-O-2 or ICD-O-3 primary site codes associated with pancreatic cancer (Table 1) (SEER, n.d.-c.).

Table 1

Primary Site Codes: Pancreatic Cancer

ICD-O-2/3 Code	Primary site
C250	Head of pancreas
C251	Body of pancreas
C252	Tail of pancreas
C253	Pancreatic duct
C254	Islets of Langerhans
C257	Other specified parts of pancreas
C258	Overlapping lesion of pancreas
C259	Pancreas, NOS

Sample and Power

The rare nature of pancreatic cancer necessitates the accurate calculation of power and subsequent selection of study participants. Several factors were considered when determining the parameters of the power analysis. Specifically, the statewide incidence rate of pancreatic cancer between 2013 and 2017 was 13.1 cases per 100,000 individuals per year, with an average annual case count of 1,556 (NCI, 2020). Given the rare nature of pancreatic cancer, the power (β) was increased from the standard level of .8 to .95 (Miller et al., 2018). An *a priori* target sample size was calculated using G**Power* (Faul et al., 2007; Faul et al., 2009). A power analysis was completed using the following criteria: 1) two-tailed, 2) α=.05, 3) Odds Ratio (effect size)=1.3, and 4) β=.95, resulting in a proposed sample size of 1,188. Study participants were selected using a random sampling strategy.

Variables and Statistical Analysis

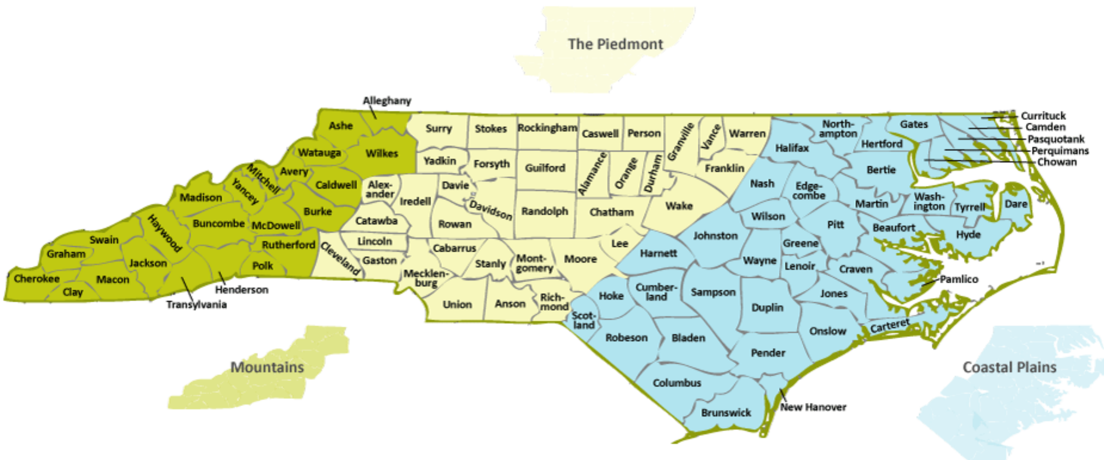
Cancer-Related Data

The pancreatic cancer obtained from the NCCCR contained 16,816 total study participant and included case-specific information about the patient's address/county at diagnosis, age at diagnosis, insurance information, primary cancer site, race, sex, diagnosis year, secondary diagnoses, and history of tobacco use. Duplicate entries were removed, resulting in a pool of 16,756 total potential study participants.

Using the county the patient resided in at diagnosis, study participants were coded to one of the regions of North Carolina: Mountain, Piedmont, or Coastal Plains. The regionalization resulted in 23 counties residing in the mountain region, 36 counties residing in piedmont region, and 41 counties residing in the coastal plains region. The data dictionary of all nominal variables included in this study can be found in Table 2.

Figure 1

Major Geographic Regions of North Carolina



Note: Adapted from *Our State Geography in a Snap: Three Regions Overview*, by the North Carolina Department of Public Instruction, 2012 (https://www.dpi.nc.gov). In the public domain.

Table 2

Data Dictionary for Nominal Variables Included in the Study

Variable name	Label	Level of measurement	Values	Missing
RGN	NC Region	Nominal	1=Mountains 2=Piedmont 3=Coastal Plains	None

Water Quality Data

Water quality data was obtained from the National Water Quality Monitoring Council's (NWQMC) Water Quality Portal (WQP) for relevant water quality factors between January 1, 2000, and December 31, 2020. The WQP is sponsored by the United

States Geological Society (USGS), EPA, and NWQMC and serves as a comprehensive repository for publicly available water quality data. The water quality factors obtained include measures of:

1. Biologicals – 70,913 results obtained for 7 factors.
2. Inorganics (minor non-metals, major non-metals, minor metals, and major metals) – 633,641 results obtained for 58 factors.
3. Nutrients – 620,582 results obtained for 28 factors.
4. Organics (pesticides, polychlorinated biphenyls [PCBs], and other) – 946,099 results obtained for 799 factors.
5. Perfluroalkyl and polyfluroakyl substances (PFAS) – 1,007 results obtained for two factors.
6. Perfleurooctanoic acid (PFOA) – 30,443 results obtained for 52 factors.
7. Radiochemicals – 3,091 results obtained for 12 factors.
8. Stable isotopes – 2,061 results obtained for 15 factors.

Water quality data obtained from the USGS were filtered to isolate North Carolina-specific data. The data files obtained included relevant information, including characteristic name, sampling strategies, dates the samples were collected, sample values, and the site-specific identifier code associated with the water quality monitoring station in which the sample was collected. Since the data files obtained did only identified site-specific identifier codes rather than county location of the water, each code had to be traced to the county of origin for each data point. Using the county in which the sample was collected, data was then categorized into one of the three geographic regions of North Carolina.

After review of the water quality data and current literature around the carcinogenic propensity of water quality factors, the following variables were selected for inclusion in the study:

- Inorganic non-metals: Arsenic, Selenium, Cadmium, Chromium
- Inorganic metals: Iron, Lead, Mercury, Zinc
- PFAS: Tetraconazole
- Organics: Carbon, Atrazine, Metolachlor, Vinyl Chloride, Inorganic Nitrogen, Kjeldahl Nitrogen, Mixed Nitrogen, Orthophosphate

Water quality variable data were combined with the pancreatic cancer database. It should be noted that water quality factors are not actively monitored in all 100 North Carolina counties. Twenty-year means were calculated for each county in which the water quality factor was monitored. The mean value for each water quality factor was added to each patient record that resided in that county upon diagnosis. For example, if a patient resided in Buncombe County at diagnosis, then the 20-year average for arsenic for Buncombe County was entered for their arsenic value in the database. Counties in which water quality factors were not monitored were coded as missing. If a water quality factor was monitored but returned a 20-year average of zero, then zero was entered as the data point and this data point was not counted as a missing value. This resulted in each pancreatic cancer patient having the relevant 20-year average value as the data point for each water quality factor monitored in the county they resided in upon diagnosis.

Statistical Analysis

The pancreatic cancer patient data was loaded into the Statistical Package for the Social Sciences (SPSS) version 27 and a random selection of 1,200 study participants were selected to accommodate for the low number of air quality sampling measures. Descriptive statistics, including frequency distributions for all categorical variables as well as measure of central tendency for all continuous variables were generated to summarize the sample population. Since the air quality data was determined to be nonparametric, a series of Kurskal-Wallis was used to determine differences in median water quality values among the different regions of North Carolina. Since the Kruskal-Wallis test only identifies the presence of a significant difference among the three regional groups, post hoc analysis using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons was performed to identify exact significant differences between the regions. For all statistical tests, assumptions were assessed, measures of effect size were calculated, and the significance threshold was set at $\alpha = 0.05$.

Results

Of the 1,200 randomly selected study participants, 147 (12.3%) were from the mountain region, 680 (56.7%) were from the piedmont region, and 373 (31.1%) were from the coastal plains region. The descriptive statistics for scale-level water quality variables include mean, median, minimum, maximum, count, and standard deviation (Table 3). It was noted that there were no recorded values for cyanide, tetraconazole, or vinyl chloride in the database. As such, continued analysis on these variables were not performed.

Table 3

Descriptive Statistics for Water Quality Variables

Water quality factor (kevel of measurement)	Mean	Median	Std. Deviation	Minimum	Maximum
Arsenic (µg/l)	0.1708	0.1013	0.1976	0.0000	1.53
Selenium (µg/l)	0.0792	0.0177	0.1947	0.0000	0.9320
Cadmium (µg/l)	0.0151	0.0078	0.0748	0.0000	1.49
Chromium (µg/l)	0.4456	0.2111	1.06	0.0000	19.78
Iron (µg/l)	1098.21	1070.98	620.64	8.95	6880.97
Lead (µg/l)	3.91	0.3637	41.65	0.000	646.00
Mercury (ng/l)	0.6048	0.3893	0.5912	0.0000	3.59
Zinc (µg/l)	11.49	10.43	9.72	0.1562	67.06
Carbon (mg/l)	416.12	5.87	4,391.52	0.000	48,298.00
Atrazine (µg/l)	5.94	0.0008	13.16	0.000	58.73
Metolachlor (µg/l)	2.60	0.0003	7.25	0.0000	67.55
Inorganic Nitrogen (mg/l)	2.26	0.6680	12.11	0.0002	109.41
Kjeldahl Nitrogen (mg/l)	0.6390	0.6574	0.2724	0.0821	1.18
Mixed Nitrogen (mg/l)	2.04	0.8785	3.13	0.0000	14.50
Orthophosphate (mg/l)	0.3715	0.0522	1.79	0.0000	15.37

Kruskal-Wallis Test

Results of the Kruskal-Wallis tests found significant differences in at least one North Carolina region for all water quality factors investigated (Table 4). Distributions of water quality values were similar, as assessed by visual inspection of a boxplot. To isolate exact median differences among the North Carolina regions, pairwise comparisons were performed in a post hoc analysis.

Inorganic Non-Metals

Median inorganic non-metal values (arsenic, selenium, cadmium, and chromium) were statistically significantly different among the regions of North Carolina. Post hoc analysis showed that piedmont region contained significantly (adjusted $p<.001$) higher median levels of selenium (*Mdn*=.0219 µg/l), cadmium (*Mdn*=.0141 µg/l), and chromium (*Mdn*=.4107 µg/l) than the mountain (*Mdn*=.0137 µg/l, *Mdn*=.0020 µg/l, and *Mdn*=.0956 µg/l, respectively) and coastal plains (*Mdn*=.0082 µg/l, *Mdn*=.0037 µg/l, and *Mdn*=.0990 µg/l, respectively) regions. The coastal plains region had significantly (adjusted $p<.001$) higher median levels of arsenic (*Mdn*=.1297 µg/l) than the piedmont (*Mdn*=.1013 µg/l) and mountain (*Mdn*=.0022 µg/l) regions.

Inorganic Metals

Median inorganic metal values (iron, lead, mercury, and zinc) were statistically significantly different among the regions of North Carolina. Post hoc analysis showed that piedmont region contained significantly (adjusted $p<.001$) higher median levels of iron (*Mdn*=1,099.80 µg/l), lead (*Mdn*=.6415 µg/l), and zinc (*Mdn*=16.52 µg/l) than the mountain (*Mdn*=440.43 µg/l, *Mdn*=.0526 µg/l, and *Mdn*=7.50 µg/l, respectively) and coastal plains (*Mdn*=1,097.28 µg/l, *Mdn*=.1916 µg/l, and *Mdn*=9.77 µg/l, respectively) regions. The coastal plains region had significantly (adjusted $p<.001$) higher median levels of mercury (*Mdn*=.5668 ng/l) than the piedmont (*Mdn*=.3120 ng/l) and mountain (*Mdn*=.4897 ng/l) regions.

Organics

Median organic values (carbon, atrazine, metolachlor, inorganic nitrogen, Kjeldahl nitrogen, mixed nitrogen, and orthophosphate) were statistically significantly different among the regions of North Carolina. Post hoc analysis showed that piedmont region contained significantly (adjusted $p<.001$) higher median levels of atrazine (*Mdn*=.0034 µg/l), metolachlor (*Mdn*=.0030 µg/l), inorganic nitrogen (*Mdn*=.7901 mg/l), and Kjeldahl nitrogen (*Mdn*=.7047 mg/l) than the mountain (*Mdn*=.0000 µg/l, *Mdn*=.0000 µg/l, *Mdn*=.3218 mg/l, and *Mdn*=.2574 mg/l, respectively) and coastal plains (*Mdn*=.0005 µg/l, *Mdn*=.0006 µg/l, *Mdn*=.3739 mg/l, and *Mdn*=.2916 mg/l, respectively) regions. The coastal plains region had significantly (adjusted $p<.001$) higher median levels of carbon (*Mdn*=7.80 mg/l), mixed nitrogen (*Mdn*=.9225 mg/l), and orthophosphate (*Mdn*=.1017 mg/l) than the mountain (*Mdn*=1.72 mg/l, *Mdn*=.4400 mg/l, and *Mdn*=.0482 mg/l, respectively) and piedmont (*Mdn*=3.85 mg/l, *Mdn*=.8785 mg/l, and *Mdn*=.0406 mg/l, respectively) regions.

Table 4

Kruskal-Wallis Results of Water Quality Among the North Carolina Regions

Water quality factor (level of measurement)	X^2	Median		
		Mountain	Piedmont	Coastal Plains
Arsenic (µg/l)	177.81^{**}	0.0022^{bc}	0.1013^{ac}	0.1297^{ab}
Selenium (µg/l)	51.28^{**}	0.0137^{bc}	0.0219^{ac}	0.0082^{ab}
Cadmium (µg/l)	155.48^{**}	0.0020^{bc}	0.0141^{ac}	0.0037^{ab}
Chromium (µg/l)	203.29^{**}	0.0956^{bc}	0.4107^{ac}	0.0990^{ab}
Iron (µg/l)	228.43^{**}	440.43^{bc}	$1{,}099.80^{ac}$	$1{,}097.28^{ab}$
Lead (µg/l)	246.89^{**}	0.0526^{bc}	0.6415^{ac}	0.1916^{ab}
Mercury (ng/l)	14.58^{*}	0.4897	0.3120^{c}	0.5668^{b}

Zinc (μg/l)	122.99**	7.50^{bc}	16.52^{ac}	9.77^{ab}
Carbon (mg/l)	460.00**	1.72^{bc}	3.85^{ac}	7.80^{ab}
Atrazine (μg/l)	237.43**	0.0000^{bc}	0.0034^{ac}	0.0005^{ab}
Metolachlor (μg/l)	182.15**	0.0000^{bc}	0.0030^{ac}	0.0006^{ab}
Inorganic Nitrogen (mg/l)	447.36**	0.3218^{bc}	0.7901^{ac}	0.3739^{ab}
Kjeldahl Nitrogen (mg/l)	362.90**	0.2574^{bc}	0.7047^{ac}	0.6916^{ab}
Mixed Nitrogen (mg/l)	131.42**	0.4400^{bc}	0.8785^{a}	0.9225^{a}
Orthophosphate (mg/l)	96.19**	0.0482^{bc}	0.0406^{ac}	0.1017^{ab}

Note: Statistically significant differences between other regions are designated by the following: ^{a}mountain, ^{b}piedmont, ^{c}coastal plains; $^{*}p<.05$, $^{**}p<.001$

Discussion

Results of this study showed significant differences between relevant water quality factors among the three regions of North Carolina. Specifically, the mountain region did not contain state-wide high levels for any water quality factor investigated. The piedmont region was noted for having the highest levels of selenium, cadmium, chromium, iron, lead, zinc, atrazine, metolachlor, inorganic nitrogen, and Kjeldhal nitrogen while the coastal plain region was noted for having the highest levels of arsenic, carbon, mercury, mixed nitrogen, and orthophosphate. Furthermore, it was noted that the piedmont region contained 66.67% (10/15) of the highest levels of water quality factors, followed by the coastal plains region (33.33% or 5/15) and the mountain region (0% or 0/15). As such, there is a significant difference among the 20-year history of water quality factors in North Carolina pancreatic cancer patients.

Regional variations in water quality factors are associated with differences in physical hydrology (precipitation, stream flow, ground water), ecology, and human impacts (climate change, industrialization, land use) (Committee on Watershed Management, 1999). However, certain insight can be gained by comparing the pattern of water quality differences with the incidence of pancreatic cancer among North Carolina regions. Specifically, the piedmont region showed the highest incidence of pancreatic cancer, followed by the coastal plains and mountain region, respectively. In the piedmont region, cadmium, chromium, iron, lead, zinc, atrazine, metolachlor, inorganic nitrogen, and Kjeldahl nitrogen showed a similar pattern of differences. Furthermore, these water quality factors were found to both align with the pattern of pancreatic cancer incidence and be significantly different among all three regions.

Inorganic Non-Metals

Cadmium and chromium are byproducts of industrialization and are known carcinogens. Cadmium increases reactive oxygen species within cells and is presumed to inactivate detoxifiers, resulting in genetic destabilization (Hartwig, 2013). While cadmium exposure is known to be associated with lung, prostate, and kidney cancers, recent evidence suggests associations with pancreatic cancer (NCI, 2022). Chromium initiates carcinogenesis through chromosomal and DNA damage (National Toxicology Program [NTP], 2021). While inhaled chromium has been shown to be associated with lung cancer, studies conducted by the NTP show that chromium exposure through drinking water is associated with alimentary canal cancers (NTP, 2021).

Inorganic Metals

Inorganic metals are often a byproduct of industrialization processes. Iron, a diverse metal that facilitates the transfer of electrons between chemicals, is critical in biological processes such as cellular respiration and energy metabolism. Cancer cells exhibit accelerated growth and metabolism, sequestering higher amounts of iron than normal cells (Mann et al., 2017). As such, increased levels of may indirectly positively influence the proliferation of cancer cells (Mann et al., 2017). Ingested lead is readily absorbed and distributed to the blood stream, where it accumulates in soft tissues (NTP, 2021). The NTP (2021) has found that exposure to lead is associated with increased risks of lung, stomach, liver, and urinary cancers. While the carcinogenicity is not fully understood, lead is thought to contribute to DNA and chromosomal damage. Zinc is an essential trace element that plays a critical role in enzymatic processes associated with cell-mediated immunity, bone/tissue growth, and brain function (Bagherani & Smoller, 2016). Contrary to other inorganic metals, numerous studies have shown zinc to support enhance immunological function of cancer patients. In their meta-analysis, Hoppe et al. (2021) found that zinc supplements reduced cancer treatment side effects in patients with head and neck cancers.

Organics

Atrazine and metolachlor are herbicides that interferes with photosynthesis in broadleaf plants (Hanson et al., 2020). Though the EPA (2022) does not consider atrazine carcinogenic, studies have found positive associations between atrazine and renal cell carcinoma (Andreotti et al., 2020) as well as pedatric cancers (Puvvula et al., 2021). The EPA has classified metolachlor as a Class C carcinogen due to the appearance of proliferative liver lesions in rats. However, Silver et al. (2015) found statistically significant positive associations between metolachlor and liver cancer among pesticide applicators.

Nitrogen is widely used in fertilizers to increase agricultural productivity. The piedmont region was found to have the highest levels of both inorganic and Kjeldahl nitrogen. When ingested, nitrogen is transformed by stomach acid into *N*-nitroso compounds (Ward, 2009), which has been shown to be associated with an increased risk of pancreatic cancer (Coss et al., 2004; Weyer et al., 2001).

Limitations

One of the biggest limitations to this study is the availability and complexity of county-level water quality data. Specifically, while the WQX contained an abundant amount of water quality data, monitoring station locations were not readily accessible. Each monitoring station was identified by an alphanumeric code (i.e., USGS-362407081153901), which had to be mapped to the county of origin for approximately 3 million data points. Complicating this matter, in many instances one monitoring station could have multiple alphanumeric codes throughout the 20-year history. While an extensive amount of time was dedicated to ensuring the accuracy, it is possible some monitoring sites were mislabeled. Additionally, the cross-sectional nature of this study provides limitations to the interpretation and use of the study information. As such, temporal or causal associations cannot be inferred from this study. Lastly, this study only investigated the association between regional water quality differences and the pancreatic cancer incidence in North Carolina. It is likely that the regional differences observed are also affected by covariates such as race, the presence of specific risk factors to pancreatic cancer, and smoking history. However, due to the nature of the data available, such investigation is beyond the scope of this study and is a recommendation for future studies.

Conclusion

Pancreatic cancer is one of the most aggressive forms of cancer and is associated with a poor prognosis for survival. Despite continued efforts to understand the etiology of pancreatic cancer, little remains known about the long-term environmental factors that place individuals at risk for developing pancreatic cancer. Results of this study showed significant, regional differences in relevant water quality factors in pancreatic cancer patients residing in North Carolina. Ten of the 15 water quality factors investigated showed statistically significant patterns that mirrored the incidence levels of pancreatic cancer across the regions of North Carolina. Of these, cadmium and forms of nitrogen (inorganic and Kjeldahl) have been shown to have significant associations with pancreatic cancer. Though they are considered carcinogens, chromium, lead, and metolachlor have not been associated with pancreatic cancer. However, given their carcinogenic nature, it is plausible that long-term exposure could play a role in the incidence of pancreatic cancer in each region. The historical presence of carcinogenic water pollutants in each region contributes to the foundation of knowledge about potential pancreatic cancer risk factors, allowing healthcare providers to understand how those risk factors may contribute to the pancreatic cancer patients in their region. As such, North Carolina healthcare providers can contextualize their approach to identifying patients at risk of pancreatic cancer earlier, promoting social change and reducing the overall mortality and morbidity of pancreatic cancer.

The findings and conclusion in this publication are those of the author(s) and does not necessarily represent the views of the North Carolina Department of Health and Human Services, Division of Public Health.

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Part 3: Summary

Integration of the Studies

The goal of this three-manuscript dissertation was to investigate the regional variability of societostructural/medical and environmental risk factors among pancreatic cancer patients in North Carolina. While previous research has provided some insight into the risk factors of pancreatic cancer, previous research has not focused on the factors that influence pancreatic cancer patients in North Carolina. Furthermore, environmental risk factors of pancreatic cancer are largely understudied. A 10-year history of pancreatic cancer data was retrospectively collected from the NCCCR. Twenty-year historical data was obtained from the EPA (air quality) and WQX (water quality). Using the county location, all data were categorized into one of three geographic regions of North Carolina: mountain, piedmont, and coastal plains. A random selection of (n=1,200) study participants was used for each manuscript. The studies used a combination of chi-square analysis, one-way ANOVA, and logistic regression for parametrically distributed data and Kruskal-Wallis tests for non-parametrically distributed data. Results from the analyses provided insight regarding the differential distribution of potential risk factors for pancreatic cancer among the different regions of North Carolina.

Common Themes/Results

Of the 1,200 randomly selected study participants, approximately 12.3% were from the mountain region, 56.7% were from the piedmont region, and 31.1% were from the coastal plains region. One common theme found across all manuscripts is the similarity between the incidence of pancreatic cancer and accumulation of significant associations. Looking at all studies, 91.4% (32/35) of the investigated risk factors showed statistically significant regional differences in North Carolina pancreatic cancer patients. The piedmont region, which had the highest incidence of pancreatic cancer, contained 59.4% (19/32) of the significant risk factors, while 28.1% (9/32) and 12.5% (4/32) of the significant risk factors were found in the coastal plains and mountain region, respectively. As such, these studies support previous research findings that the accumulation of risk factors may contribute to the manifestation of pancreatic cancer. (Knechtges et al., 2018). The combination of these studies also facilitates the creation of portfolio of unique exposures for pancreatic cancer patients in each region.

Mountain Region

Pancreatic cancer patients in the mountain region were .22 times (95% CI=.09-.57) less likely to be Black and .60 times (95% CI=.43-.85) less to have a history of diabetes when compared to pancreatic cancer patients in other regions. Furthermore, pancreatic cancer patients in the mountain region were exposed to significantly higher levels of NO_2 (*Mdn*=10.97 ppb), PM_{10} (*Mdn*=18.37 μg/m^3), benzene (*Mdn*=2.28 ppb), and ethylbenzene (*Mdn*=.6344 ppb) when compared to pancreatic cancer patients in other regions. The mountain region did not show significantly higher levels of any water quality factor investigated.

Piedmont Region

Pancreatic cancer patients in the piedmont region were .07 (95% CI=.01-.55) less likely to be Native American/Alaskan Native, and .79 times (95% CI=.67-.93) less likely to have a history of smoking. However, they were 1.33 times (95% CI=1.01-1.75) more likely to have a history of pancreatic disorder, 2.26 times (95% CI=1.03-4.96) more likely to have a history of biliary system disorders, 1.87 times (95% CI=1.01-3.44) more likely to have a history of esophageal disorders, and 2.27 times (95% CI=1.42-3.65) more likely to have a history of signs and symptoms than their counterparts in other North Carolina regions. Furthermore, pancreatic cancer patients in the piedmont region were exposed to significantly higher levels of AQI (*Mdn*=52.57), O_3 (*Mdn*=.03352 ppm), SO_2 (*Mdn*=1.52 ppb), $PM_{2.5}$ (*Mdn*=10.88 μg/m^3), NO (*Mdn*=4.22 ppb), selenium (*Mdn*=.0219 μg/l), cadmium (*Mdn*=.00141 μg/l), chromium (*Mdn*=.4107 μg/l), iron (*Mdn*=1,099.80 μg/l), lead (*Mdn*=.6415 μg/l), zinc (*Mdn*=16.52 μg/l), atrazine (*Mdn*=.0034 μg/l), metolachlor (*Mdn*=.0030 μg/l), inorganic nitrogen (*Mdn*=.7901 mg/l), and Kjeldahl nitrogen (*Mdn*=.7047 mg/l) as compared to pancreatic cancer patients in other regions.

Additionally, given the overall high incidence of pancreatic cancer in the piedmont region, the identified risk factors from these studies may provide insight as to relevant risk factors of pancreatic cancer, guiding future research efforts. Specifically, these studies identified significant findings associated with previous medical histories and known carcinogenic agents ($PM_{2.5}$, cadmium, chromium, lead, metolachlor, and nitrogen). Given the ambiguity surrounding the risk factors of pancreatic cancer, future research around these factors may provide additional relevant insight into the etiology of pancreatic cancer.

Coastal Plains

Pancreatic cancer patients in the coastal plains region were 1.87 times (95% CI=1.51-2.30) more likely to be Black, 14.34 times (95% CI=3.8-53.7) more likely to be American Indian/Alaskan Native, 1.41 times (95% CI=1.16-1.70) more likely to have a history of smoking. However, they are .52 times (95% CI=.34-.78) less likely to have a history of biliary system disorders and .57 times (95% CI=.44-.74) less likely to show signs and symptoms when compared to pancreatic cancer patients in other regions. Pancreatic cancer patients in the coastal plains were exposed to significantly higher levels of CO (*Mdn*=.63412 ppm), Pb-$PM_{2.5}$ (*Mdn*=.0022 μg/m^3), arsenic (*Mdn*=.1297 μg/l), mercury (*Mdn*=.5668 ng/l), carbon (*Mdn*=7.80 mg/l), mixed nitrogen (*Mdn*=.9225 mg/l), and orthophosphate (*Mdn*=.2027 mg/l) when compared to pancreatic cancer patients in other regions.

Positive Social Change

As the incidence of pancreatic cancer continues to grow, the investigation of pancreatic cancer risk factors presents a viable opportunity to reduce the mortality and morbidity associated with the disease. The results of these studies identified regional-specific differences among potential risk factors in pancreatic cancer patients. As such, medical professionals in North Carolina have a better understanding of the regional risk factors that influence pancreatic cancer within their communities. Given that modern science has yet to resolve the challenges associated with the early detection of pancreatic cancer (Henrikson et al., 2019), a more comprehensive understanding of regional risk factors for pancreatic cancer promotes positive social change by facilitating early detection strategies, such as targeted public health campaigns, screening opportunities, and advocacy, potentially decreasing the economic and social burden of pancreatic cancer.

Future Research

There remains a need to continue investigating the associations between societostructural, medical, and environmental risk factors and pancreatic cancer. While societostructural and medical risk factors of pancreatic cancer have been well studied, the results have yet to identify conclusive evidence as to their direct relationship with pancreatic cancer etiology. Furthermore, the association between environmental risk factors and pancreatic cancer is grossly understudied. Evidence from toxicology studies show relevant environmental factors are not only capable of carcinogenesis, but also associations to other forms of cancer. While this research identified associations between certain environmental factors and pancreatic cancer, future research may clarify the exact relationship between these factors and pancreatic cancer.

The literature review conducted showed the majority of pancreatic cancer risk factor research investigates global or national epidemiological trends of pancreatic cancer. While these studies provide a generalized approach to pancreatic cancer research, regional-specific epidemiological trends may be masked. As such, future research should investigate regional differences in risk factors to build upon the knowledge from studies spanning large geographic areas.

The use of geospatial statistical techniques could greatly enhance the investigation of regional risk factors of pancreatic cancer. Such research would be useful in the investigation of both societostructural/medical risk factors as well we environmental risk factors of pancreatic cancer. Geospatial techniques facilitate the overlay of pancreatic cancer cases and risk factors, modeling how spatial trends in risk factors impact the pattern, risk, and distribution of pancreatic cancer.

Lessons Learned

This dissertation used publicly available information from the USGS and EPA. The 20-year history investigated provided almost four million data points for 1,095 environmental factors. Most of these data had to be carefully reviewed and matched to their respective county in North Carolina. Doing this, I learned the importance of establishing strategies to ensure the data clean-up was performed accurately. Furthermore, the work presented in this dissertation investigated only 30 factors. As such, there presents a tremendous opportunity to continue researching environmental factors associated with pancreatic cancer.

Conclusion

Though rare, pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States, killing 90.7% of individuals diagnosed within 5 years. Despite this, knowledge about the risk factors and causes of pancreatic cancer remain elusive. This dissertation conducted a series of three quantitative studies investigating the regional associations between pancreatic cancer and societostructural and environmental risk factors in North Carolina. Societostructural/medical risk factors such as race and history of relevant gastrointestinal diseases were statistically significantly different among pancreatic cancer patients in the three regions of North Carolina. Specifically, these studies identified significant findings associated with previous medical histories and known carcinogenic agents ($PM_{2.5}$, cadmium, chromium, lead, metolachlor, and nitrogen). Given the ambiguity surrounding the risk factors of pancreatic cancer, future research around these factors may provide additional relevant insight into the etiology of pancreatic cancer.

The findings and conclusion in this publication are those of the author(s) and does not necessarily represent the views of the North Carolina Department of Health and Human Services, Division of Public Health.

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