

A Quantitative and Spatial Analysis of Pancreatic Cancer in South-Central
Appalachia

A Dissertation Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

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May 2023

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DEDICATION

The enclosed work is dedicated first and foremost to my wife, Susan, and my children, Benjamin and Henry. You have been my support, foundation, and motivation while I worked for my Ph. D. and remained a full-time clinician over the last three years during a global pandemic. Benjamin and Henry, I hope my determination and ethic inspire you to work hard for your dreams. Never forget; anything is possible with hard work and the love and support of your family!

This work is also dedicated to the pancreatic cancer patients I have had the opportunity to serve and care for over the last ten years. There are very few glimpses of hope for these patients, and yet I have been impressed time and time again by the strength of the human spirit demonstrated by the brave individuals who face this diagnosis and choose to fight despite overwhelming odds. I have sat face-to-face with patients too many times to count and told them about their diagnosis for the first time and the prognosis associated with it. Too often, I have broken the news that something new has been found on a scan, a tumor marker has elevated, or we have exhausted all options. I have helped patients and their families decide to meet with hospice and sat through many funerals. This disease is indiscriminate in who it affects. I have cared for older patients who have lived rich and full lives before their diagnosis, and I have cared for patients younger than me and gotten to know their children. I can still see their faces. This is my small effort to affect pancreatic cancer for my community

at a larger scale than one-on-one, as I can do clinically. This is my effort to improve prognosis for the future through awareness and increased knowledge.

ACKNOWLEDGEMENTS

I must acknowledge my dissertation Chair, Dr. Tami Wyatt. Without Dr. Wyatt's support, encouragement, and guidance, I would not have returned for my doctorate, let alone completed this work! In truth, Dr. Wyatt is more than just the chair of my dissertation committee; she is a longtime friend, and I am fortunate to have the opportunity to learn from and work with her. I also wish to acknowledge Dr. Sadie Hutson. Dr. Hutson's guidance has been critical to my academic success throughout the doctoral program. I must acknowledge my committee members, Dr. Sangwoo Ahn, Dr. Laura Enomoto, and Dr. Karen Lasater. Thank you for your guidance and support throughout my research.

I must also acknowledge my clinical colleagues - specifically Dr. James Lewis, Dr. James McLoughlin, Dr. John Bell, and Dr. Laura Enomoto. Thank you for supporting my decision to resume my education while continuing to work and trusting that I could provide high-quality care to our patients while enrolled full-time as a graduate student. The last three years in the healthcare environment have had more trials and tribulations than I have seen throughout my career; being a student and a full-time clinician during this time has been a challenge! I appreciate your support and encouragement to expand my horizons so that I can impact patient care on a new level in the future and continue to benefit our community.

Finally, I wish to acknowledge Dr. Sapna Syngal and Dr. Nicolette Rodriguez of Dana Farber Cancer Institute/Harvard School of Medicine, Dr. Tara

Coffin of University of Washington, Dr. Alison Rosenzweig of PanCAN and Dr. Barbara Kenner of the Kenner Family Foundation for their mentorship and support. Dr. Syngal generously welcomed me into her research group during the height of the pandemic without meeting me in person. Being a part of this wonderful multi-disciplinary team has been an invaluable education. I look forward to future collaborations to improve the prognosis for pancreatic cancer patients no matter where they are, where they are from, or what they look like. I cannot begin to acknowledge how much I have learned from these brilliant scientists and clinicians, and I am honored to work with you and look forward to future collaborations.

PREFACE

The scope of this dissertation is to fulfill the requirements of the Doctor of Philosophy (Ph.D.) degree from the College of Nursing. This work represents the manuscript dissertation option and includes a state of the science/literature review of pancreatic cancer as chapter two, a detailed description of the materials and methods in chapter three, a descriptive and quantitative analysis of pancreatic cancer demographics and mortality in South-Central Appalachia as and the spatial distribution of pancreatic cancer and its' influence on survival in South-Central Appalachia as chapter four. This work intends to bring attention to pancreatic cancer, highlight how pancreatic cancer impacts a specific region within the United States (US), and explore how spatial location affects outcomes in this aggressive disease. The goal of this work is to raise awareness (for patients, providers, and the public) for pancreatic cancer and demonstrate the impact of cancer on the Appalachian region of the US and explore novel approaches to secondary data analysis. Meeting these goals will open future research opportunities. If pancreatic cancer awareness is improved and even one patient has their pancreatic cancer identified earlier by the knowledge generated by this study, then this study is a success. May this work be a small step toward improving the prognosis for this grim disease.

ABSTRACT

Pancreatic cancer (PC) has a grim prognosis and is the third leading cause of cancer death in the United States. Patients with the best prognosis are those who are found with the disease at a stage early enough to be surgically resectable. No current strategies to identify PC early, outside of specific high-risk individuals, exist. This study described population demographics for PC patients in South Central Appalachia, identified healthcare and demographic variables that will aid in early PC identification, and assessed patient location as a significant independent variable in predicting PC outcomes.

A retrospective analysis of tumor registry and electronic health record data on PC patients at an academic medical center in South Central Appalachia with a high-volume pancreas service was completed. Data from 2010 through 2020 were analyzed. Statistical analysis for descriptive and inferential statistics were completed using SPSS v. 29 for Macintosh. Spatial analysis was conducted using ArcGIS Pro 3.0.

The sample revealed a total of 931 individuals with pancreatic cancer. The mean age of diagnosis was 67.0; 52% were male, 89.8% of individuals identified as white. 69.8% presented with Stage IIb, III, or IV disease. The mean distance to the treatment facility was 56.6 miles, the mean driving time was 49.8 minutes. Significant variables associated with disease prognosis include distance to the facility; having a primary care provider, having insurance, and mortality could be predicted both by stage of disease at the time of diagnosis and insurance status.

Distance to the high-volume PC treatment center was found to serve as facilitator to an earlier time to treatment and early stage of diagnosis when patients live closer to the high-volume treatment center.

Secondary analysis of regional PC patient characteristics can be informative in identifying non-biological variables associated with disparate outcomes. This regional perspective can be valuable in identifying areas for healthcare resource investment to improve outcomes. Knowledge from this study will serve future nurse scientists interested in PC, and the methodology used by this study remains a powerful tool for future nurse scientists to use across the healthcare spectrum to understand how spatial location influences health outcomes.

TABLE OF CONTENTS

CHAPTER I INTRODUCTION	1
Background	2
Purpose of Study	4
Specific Aims	5
Broader Implications of Research	5
Significance	6
Significance to Nursing	6
Theoretical Framework	8
Nursing Philosophy	8
Behavioral Model for Vulnerable Populations	9
Assumptions	15
Research Questions	15
Definition of Terms	16
Limitations/Delimitations	16
Summary	17
References	19
Appendix	26
CHAPTER II THE FIRST ARTICLE & LITERATURE REVIEW	27
Abstract	28
Introduction	29
Prevalence	29
Identification of PDAC	30
Hereditary Risk Factors	31
Genetic Predisposition Syndromes	32
Recommendations	35
Conclusion	36
References	38
Appendix	46
CHAPTER III SYNTHESIS OF THE PANCREATIC CANCER (PC) LITERATURE 2022 - 2023	76
Introduction	78
Results	82

Clinical Application.....	84
Gene Identification.....	84
High-Risk Screening.....	86
Therapeutic Applications	89
Discussion.....	91
References.....	92
Appendix	99
CHAPTER IV MATERIALS AND METHODS.....	100
Introduction	102
Study Aims	102
Materials and Methods	103
Study Design	103
Inclusion/Exclusion Criteria.....	103
Ethics Approval.....	104
Data Sources	104
Statistical Plan	105
Data Security/Confidentiality.....	107
Discussion.....	108
Conclusion	108
References.....	110
Appendix	113
CHAPTER V IMPACT OF HEALTHCARE ACCESS ON PANCREATIC CANCER OUTCOMES in SOUTH-CENTRAL APPALACHIA.....	114
Abstract.....	115
Introduction	117
Background and Significance	117
Research Design and Methods	121
Conceptual Framework.....	121
Methodological Approach	123
Data Collection	123
Data Analysis.....	125
Results	126
Implications	129
References.....	133

Appendix	140
CHAPTER VI PANCREATIC CANCER IN SOUTH-CENTRAL APPALACHIA: THE GOOD, THE BAD, AND SILVER LINING	147
Abstract	148
Introduction	150
Methods	152
Results	155
Implications	156
References	162
Appendix	167
CHAPTER VII CONCLUSION & DISCUSSION	183
Conclusion	184
Implications for Practice	192
Implications for Policy.....	196
Implications for Future Research.....	198
Broader Implications of the Current Study.....	200
Strengths and Limitations.....	201
Discussion	203
Contribution to Nursing	204
References	207
VITA.....	212

LIST OF TABLES

TABLE 1 DEFINITION OF TERMS	26
TABLE 2 PANCREATIC SCREENING RECOMMENDATIONS (ADAPTED FROM NCCN VERSION 1.2022)	47
TABLE 3 LITERATURE REVIEW MATRIX – GERMLINE GENETIC APPLICATION TO HIGH- RISK SCREENING AND MANAGEMENT IN PANCREATIC CANCER.....	49
TABLE 4 ICD 9 AND ICD 10 CODES.....	113
TABLE 5 INCIDENCE AND FIVE-YEAR MORTALITY CHARACTERISTICS PANCREATIC CANCER COMPARED TO TENNESSEE TUMOR REGISTRY DATA** AND NATIONAL TRENDS (SEER)***	141
TABLE 6 2010 – 2020 SOUTH CENTRAL APPALACHIA PANCREATIC CANCER POPULATION DESCRIPTIVE SUMMARY, INCLUDING ANDERSEN’S BMVP ENABLING FACTORS.....	142
TABLE 7 ANDERSEN’S BEHAVIORAL HEALTHCARE ACCESS MODEL FOR VULNERABLE POPULATIONS: PANCREATIC CANCER PATIENTS IN SOUTH-CENTRAL APPALACHIA ANDERSEN’S HEALTHCARE ACCESS AND NEED FACTORS.....	143
TABLE 8 PANCREATIC CANCER COHORT ATTRIBUTES (2010 – 2020 SOUTH-CENTRAL APPALACHIA HIGH-VOLUME TREATMENT CENTER).....	181

LIST OF FIGURES

FIGURE 1 PRISMA FROM INTEGRATIVE REVIEW OF GENOMICS IN PANCREATIC CANCER	48
FIGURE 2 PRISMA FROM INTEGRATIVE REVIEW UPDATE: GENOMICS IN PANCREATIC CANCER	99
FIGURE 3 CONCEPTUAL FRAMEWORK	140
FIGURE 4 REGIONS OF APPALACHIA.....	144
FIGURE 5 DISTRIBUTION OF STUDY PARTICIPANTS	145
FIGURE 6 LOCATION OF HIGH-VOLUME PANCREATIC CANCER TREATMENT CENTERS (US)	146
FIGURE 7 ARCGIS MAP DEMONSTRATING PANCREATIC CANCER PATIENT DISTRIBUTION AND 30, 60, AND 90-MINUTE DRIVETIME.....	167
FIGURE 8 KAPLAN MEIER FIVE-YEAR SURVIVAL CURVE (OVERALL SURVIVAL BY TRAVEL TIME TO HIGH-VOLUME PC TREATMENT CENTER).....	180

CHAPTER I INTRODUCTION

Background

Pancreatic cancer (PC) has a dire prognosis. The majority of PC is ductal adenocarcinoma and associated subtypes (approximately 85%) while a small percentage of PC is associated with neoplasms from the endocrine pancreas including several subtypes of neuroendocrine tumors (Badheeb et al., 2022). When PC incidence and outcomes are reported, these figures represent all forms of PC unless otherwise specified. PC is the third principal cause of cancer mortality in the US, with an incidence rate of 13.7 and 10.7 (per 100,000) in males and females, respectively (Niederhuber et al., 2013; Siegel et al., 2022; Wilson et al., 2016). Approximately 62,000 patients will be diagnosed with PC annually in the US (Siegel et al., 2022). PC often affects individuals after age 45, but younger diagnoses occur. As of 2022, men are more often afflicted than women (1.3:1), and Black Americans have poorer outcomes than White Americans diagnosed under similar circumstances (McWilliams et al., 2018). Historically, PC presents too late for surgical intervention because there are no generally available screening tests, and the disease is often no longer operable when a patient is symptomatic. As a result, only a small proportion of patients diagnosed with PC will have a 30% survival prognosis.

Incidence of PC in South-Central Appalachia is like that of the US overall, with southern Appalachian men affected by PC at a rate of 13.7 and women at 10.2 (per 100,000), and central Appalachian men affected at a rate of 12.8, and women at 9.5 (Wilson et al., 2016). For those patients who complete surgical

resection and have adjuvant systemic therapy, such as chemotherapy and regional radiation therapy, the five-year survival rate is at best 30% when there is no nodal involvement. This is further reduced to 10% if nodal disease spread is present (Niederhuber et al., 2013). Clearly, early identification of PC is a key element for improving the prognosis of this disease. Mortality for PC in the US for 2022 is projected to be 80.1%, while mortality for PC in Tennessee from 2014 – 2018 was 89% (Richards & Whiteside, 2022; Siegel et al., 2022).

Individual risk factors for PC include such modifiable lifestyle factors as tobacco use, obesity, physical inactivity, a diet high in saturated fats and processed meats, excess alcohol consumption, a personal history of pancreatitis, and diabetes mellitus with insulin resistance (Bosetti et al., 2012; Carreras-Torres et al., 2017). Heredity also plays a significant role. These factors include a family history of PC and genetic predisposition disorders (Grant et al., 2015; Shindo et al., 2017).

PC is rare compared to breast or colon cancer, yet far more lethal, as established above. As a result, there are no population-level screening recommendations for PC. Historically, PC treated at high-volume centers with increased access to imaging, a gastroenterologist who provides advanced endoscopy, and specialists in treating PC, including surgical specialists, has the best outcome (Ratnayake et al., 2022). Previous studies have demonstrated that demographic and social factors significantly affect access to high-volume

centers, including race/ethnicity and insurance status (Bui et al., 2022; Ratnayake et al., 2022).

Purpose of Study

This study was designed to quantitatively analyze the individuals affected by PC in South-Central Appalachia by examining the population served by a high-volume academic medical center for demographic characteristics and overall outcomes. No previous work has described this specific geographic population with PC. Long-term goals for this study include increasing awareness of PC and improving the prognosis by helping patients and providers recognize who is at increased risk of the illness and early identification of the signs and symptoms. Studies have shown an earlier stage of diagnosis equates to an improved prognosis (McGuigan et al., 2018). This study identified barriers and facilitators to care for PC in South-Central Appalachia. Dissemination of the findings from this study will support the long-term goal of increasing awareness of the disease and improving prognosis by helping to identify PC at earlier stages. Results from this study will also be helpful in policy updates to improve equity in healthcare access in South-Central Appalachia. The dissertation accomplished these goals through the following specific aims and broader research implications.

Specific Aims

- Describe the population demographics for PC patients in South-Central Appalachia.
- Assess healthcare and demographic variables for PC patients in South-Central Appalachia for trends over time and space.
- Use ArcGIS to determine if the patient's location is a significant independent variable in predicting PC outcomes.

Broader Implications of Research

- Provide a model for describing regional attributes of cancer patients that serve as barriers and facilitators independent of tumor biology
- Contribute to a better understanding of identifying individuals at increased risk of PC to detect disease earlier when the prognosis is better
- Provide a model to predict which individuals can be identified at increased risk of PC in the primary care setting for nurse practitioners
- Identify barriers and facilitators to cancer care in South-Central Appalachia to help direct future healthcare policy
- Identify the critical role of primary care and how advanced practice nurses can help provide these services and increase population health, including cancer care, as a result

Significance

The significance of this work is two-fold. First, the South-Central Appalachian population with PC has not been previously described in great detail (Deddabasappa et al., 2006; Wilson et al., 2016). PC has its inherent biological challenges, and it is unclear to what degree these are affected by regional variation in access to care. By describing this population in detail within the context of South-Central Appalachia, this work contributes valuable knowledge that will impact future patient care for the region. The second significant aspect of this work is that it serves as an example for future research into specific cancer diagnoses for the region. This framework can serve as a template for regional approaches to individual cancer diagnoses or even national-level approaches. Understanding how local and regional variation affects cancer prognosis will be a valuable step towards providing personalized or precision care in the future. Regional factors of healthcare access and chronic disease can have a positive or negative influence on prognosis that is independent of biological factors. Yet, this influence remains poorly defined or understood, and the unique regional attributes are often not a component of, or not incorporated into, clinical practice.

Significance to Nursing

In addition to being a significant study to generate new PC knowledge and serving as an exemplar for its novel quantitative methodological approach using both statistical analysis and spatial analysis, this study has significance for the

discipline of nursing as well. Beginning with the clinical significance, advanced practice nurses working in primary care or specialty care will benefit from new knowledge regarding identification of PC and best-practice referrals of PC to the appropriate specialists. Advanced practice nurses and students working toward their clinical doctorate, can use the knowledge generated in this study to design and implement evidence-based practice improvements.

For nurses working in oncology, especially nurse navigators responsible for new patient intake and navigating patients to the appropriate oncology specialists, the knowledge generated from this study will help to stratify patients based on risk and will provide an evidence-base for improving patient triage. Furthermore, nurses working in oncology can use the findings from this study to appropriately plan and implement care plans based on risk factors that are pertinent to their population. From a holistic-care standpoint, nurses caring for PC patients in South Central Appalachia will be able to approach care from an entirely new perspective that personalizes their approach to the region.

Nurse scientists stand to benefit from the findings of this study by understanding how the methodology demonstrated in this work has the potential to be applied to any regional population and virtually any diagnosis of interest. For nurse scientists focused on answering research questions best addressed by quantitative and/or mixed methods research methods, this study represents a powerful approach to data science that is accessible and broadly applicable. For nurse scientists using qualitative methods to understand a scientific

phenomenon, the knowledge demonstrated by this study can serve as a springboard for qualitative study design by providing a foundation to both characterize the population presented, but also by identifying areas for qualitative inquiry.

Theoretical Framework

Nursing Philosophy

The philosophical foundation for this study is firmly grounded in pragmatism and the ethos of need for critical inquiry, plurality, and change. From an epistemology perspective, this study investigated the overall experience of PC patients in South-Central Appalachia based on shared health variables; whether this be access to health via primary care or health insurance or presence and absence of chronic disease known to be high risk factors for PC. Much like Hartrick-Doane and Varcoe (2005) and their approach to family nursing, this study seeks to conceptualize PC in a way that will benefit both individuals affected by PC as well as the clinicians providing their care. This inquiry was undertaken with the hypothesis that spatial location alone could have an influence on outcomes associated with PC such as overall survival and mortality; after all, the biology of the disease is not geographically dependent. In other words, this study examined PC in South-Central Appalachia and to do this required inquiry into what PC in Appalachia looks like, essentially the pragmatic theory of truth attributed to William James (Chisholm, 1992). Therefore, the

methodological approach chosen for this study was a quantitative one using retrospective, secondary data. A quantitative prospective study or a qualitative study would not be pragmatic due both to the poor prognosis associated with PC and the timeline associated with completing a dissertation level study.

Behavioral Model for Vulnerable Populations

The Andersen Model of Health Services Utilization (MHSU), developed initially in the 1960s as the Behavior Model of Families' Use of Health Services by Ronald Andersen through his dissertation work is the underlying framework for this study (Anderson, 1968). Over time, the MHSU has become a more specialized model that can be applied to vulnerable populations (Andersen, 1995; Gelberg et al., 2000). Andersen describes, in his 1968 dissertation work, how he developed the model to answer how and why individuals use health services using secondary data (Andersen, 1995). The model transitioned from focusing on the family unit to concentrate on the individual because of the complexity involved in accounting for family health status versus the relative ease of accounting for an individual's health status. The initial model demonstrates that using health care services depends on one's predisposition to use such services and factors that impede the use of health services; this evolved into the MHSU.

The MHSU provides a framework by which health behaviors are understood by looking at individual attributes and circumstantial determinants of

health. The model demonstrates how healthcare utilization, for example, can be influenced by predisposing, enabling, and health need factors (Andersen, 1995; Babitsch et al., 2012). Predisposing factors include age, gender, education, occupation, ethnicity, family status, region of residence (urban, rural, or neighborhood), and various characteristics of health beliefs. Enabling factors, or those attributes attributed to increasing healthcare access, include economic and access factors. Enabling factors are positive attributes when they are present, and they are obstacles to healthcare access when they are absent. Economic factors include income, employment status, and health insurance status.

Health access factors include factors such as having access to a regular source of health care, once again regionality (urban vs. rural), and having the means to access available care, e.g., transportation to and from healthcare appointments. The need factors within the Andersen model are divided into individual and environmental need factors. Individual needs include how individuals view their health status and the presence or absence of illness, including chronic disease (e.g., hypertension, diabetes). Put simply, what are the health factors that would drive an individual need to access healthcare? Does a patient have hypertension or diabetes that requires healthcare management? If yes, then these chronic disease diagnoses are individual need factors. The environmental factors include looking at occupation, crime, and community traffic-related injury and death rates. The environmental need in population indices includes mortality, morbidity, and disability levels within a community. For

example, an individual living in a non-metropolitan area who cannot easily access a primary care provider because the individual does not possess their own transportation and does not have access to public transportation may not have the same opportunity for healthcare access as an individual who lives in an urban community with ready access to public transportation. Another example would be an individual who lives in a community with few choices in primary care providers, all of which will not see the individual unless they have specific health insurance coverage. Their environment's lack of choice or options represents a significant obstacle to their healthcare access.

In 2000, Andersen and colleagues developed the Behavioral Model for Vulnerable Populations (BMVP) in response to contemporary reductions in benefits to vulnerable individuals such as minorities, immigrants, children, the elderly, the mentally ill, and economically disadvantaged individuals (Gelberg et al., 2000). The BMVP built upon the prior MHSU by including attributes or “domains” specific to vulnerable populations, such as immigration status, receipt of public benefits, and diagnoses associated with vulnerability (acquired immunodeficiency syndrome or AIDS, for example) within the predisposing, enabling, and need factor categories respectively.

Andersen’s model, specifically the BMVP version, is an ideal foundation for understanding health behaviors through secondary data and specifically for the study represented here on PC in South-Central Appalachia (Brown et al., 2004). Secondary data provides a variety of variables, many of which represent

the predisposing, need, and enabling factors and can be used to understand healthcare access behaviors. My dissertation research focused on understanding health behaviors in a specific vulnerable population, patients with PC in South Central Appalachia. The research was accomplished using tumor registry data collected at a large academic medical center with a high PC volume. More specifically, my proposed research population has an added level of vulnerability by its location within the United States (US), South-Central Appalachia, as defined by Roberson et al. (2021), whose study with breast cancer patients occurred in the same academic medical center. This region has historically been portrayed as vulnerable because of its remote geographic location and lack of accessible healthcare providers (Abdoli et al., 2017). The MHSU model from Andersen has been applied by researchers (Ahn et al., 2022, Baedke et al., 2022) previously to secondary data analysis, and these prior studies serve as an example for approaching PC tumor registry data. For these reasons, the BMVP will serve as the theoretical underpinning of this study.

There were multiple strengths to using the BMVP model from Andersen for secondary data analysis, specifically tumor registry data. First, variables from the retrospective sample of tumor registry data include many of the predisposing, enabling, and need factors and access variables described by Babitsch et al., (2012) in their meta-analysis of Andersen's model. These data required no manipulation or alteration, increasing internal and external validity. Further, the BMVP version of Andersen's model is relevant to the vulnerable nature of the

study population based on having a PC diagnosis and residing in South-Central Appalachia. Finally, an intended strength of using the Andersen model is assessing healthcare access based on objective data with pragmatic implications. This strength can be helpful when appealing to policymakers and advocating for this vulnerable population based on study findings.

Variables for this study were selected using the meta-analysis of Andersen's MHSU from Babitsch et al. (2012), with vulnerable population factors selected as defined by Gelberg et al. (2000). Predisposing demographics, including age, gender/sex, ethnicity, and region of residence, were selected. In addition to providing demographic factors needed to describe the population of PC patients, the region of residence is a key enabling variable and will help to identify access elements such as driving time and driving distance for each patient. Region of residence will also provide a continuous variable (distance defined as miles to treating facility from residence and driving time specified in minutes' drive time to treatment facility) for statistical analysis. Enabling factors selected to include insurance status, having a primary care provider (PCP), and patient location. Need factors, individual health factors requiring healthcare access, chosen for this study include patient BMI and co-morbidities including depression, diabetes, heart disease, hypertension, hyperlipidemia, obesity (as noted in the chart review independent of BMI), history of pancreatitis, history of alcohol abuse, and history of tobacco use.

Geographical Information Services (GIS) software was used to augment the data variables attainable from the tumor registry and the electronic medical records. GIS allowed for novel variables such as patient location and travel time to the treating facility to understand the ratio of metropolitan versus non-metropolitan PC individuals and whether this is a significant factor in healthcare access. The distance to a facility (academic medical center) variable is available on all individuals from the tumor registry. This creates a unique variable to assess the impact of patient location on healthcare access and helps evaluate how the region of residence affects the stage of presentation and overall prognosis of PC for the specified population. Enabling factors from the tumor registry include health insurance status if the individual has a primary care provider (PCP), employment status, and region of residence. Evaluation of these enabling factors will help to determine if they have a positive impact on healthcare access for PC patients by examining time to treatment (time from diagnosis to time of initial active therapy), stage of PC upon presentation (AJCC 8th edition), and overall survival as measured by time (months) and survival (alive versus deceased). Need factors available from the tumor registry used in this research include concomitant diabetes, hypertension, heart disease, hyperlipidemia, and obesity. Additional need factors include tobacco use, alcohol abuse, and body mass index (BMI). Evaluation of these need factors helped identify which chronic diseases are associated with either a positive or negative influence on prognosis for PC patients and can be compared to previously

established risk-factors for PC from the literature. Healthcare access factors available included whether the patient had a PCP or not at the time of their PC diagnosis. Having a PCP helped to identify if there are disparate outcomes between patients with a PCP and those without when evaluating the stage of presentation, time to treatment, and overall survival for the sample population.

Assumptions

- Individuals living further from the high-volume academic medical center will have decreased access to primary care
- Individuals living further from the high-volume academic medical center will present with more advanced-stage PC
- Individuals with inadequate health insurance (uninsured, Medicare, Medicaid) will present with more advanced-stage PC and this will lead to decreased overall survival
- Individuals with comorbidities considered to be risk factors for PC will present with later-stage PC and have increased morbidity and mortality

Research Questions

- What are the characteristics of PC patients in South-Central Appalachia?
- What are the barriers and facilitators to care for PC patients in the study region?

- How does the disease presentation and survival of the study population compare to the overall US population?
- Is access to healthcare a significant factor (independent of tumor biology) in overall survival?

Definition of Terms

Several terms are vital concepts throughout the study. These terms may not be familiar to those unfamiliar with caring for individuals with PC provided in Table 1. All tables and figures are included in the appendices at the end of the chapters.

Limitations/Delimitations

Several limitations are associated with MHSU/BMVP. First, many of the factors are categorical type data. As a result, the breadth of inferential statistical analyses was limited due to few continuous independent variables. Another limitation of this Andersen model-driven research is that results from the study may not be generalizable to areas other than South-Central Appalachia, given this region's unique vulnerabilities and limited resources. Finally, an additional limitation to using MHSU as a guiding framework is that many factors attributed to personal perceptions of health and health behavior beliefs are unavailable within the tumor registry. This restricts the proposed research's overall scope and potential statistical studies used.

Additional limitations are associated with using ArcGIS to analyze the data. While this powerful tool provides unique insights into any dataset, using ArcGIS to its full potential requires street-level addresses for each patient, which may not always be available. Finally, this study is purely quantitative in nature with no qualitative component. Findings from this study are generalizations on how the selected independent variables influence healthcare access and PC outcomes; no data is present to reflect individual patient-level decisions or patient perceptions of barriers to healthcare access.

Delimitations include the proposed study focusing only on PC and individuals treated for PC at a single high-volume institution where the author is employed. The study focused on a defined period, 2010 through 2020. Finally, patients in the study population were not active clinical patients for the investigator, and the investigator is not a part of these patients' current clinical care. This was a critical delimitation to help reduce intrinsic bias.

Summary

PC is a lethal cancer diagnosis that is seemingly indiscriminate in its impact on the patients who live with the disease. This study describes the South-Central Appalachian population of the US who have been diagnosed with PC for the first time. In addition to describing the PC population, this study design included evaluating how individual modifiable and non-modifiable attributes impact the stage of presentation, time to treatment, and overall survival using the

Andersen BMVP for healthcare access. Finally, this study used a novel analytical approach by applying GIS software to secondary data to explain how spatial factors may influence healthcare access in the PC population of South-Central Appalachia. The knowledge generated by this approach serves to provide an example for future studies, help explain how healthcare access can impact healthcare outcomes in a unique population and help inform healthcare decisions and policy positions.

The following study will first be contextualized by a practice update and literature review. Then, a chapter devoted to describing the materials and methods will describe the study design, inclusion and exclusion criteria, ethical approval, data sources, power calculations, statistical plan, and data security. Then, two manuscripts examining health access behaviors of South-Central Appalachia PC patients and role of spatial location in PC outcomes are provided. Finally, the dissertation will end with a conclusion that includes implications of the study results, potential for future research, how the study outcomes affect nursing, how the findings are congruent with existing knowledge, and how study findings reveal what factors PC patients can control.

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Appendix

Table 1 Definition of Terms

Term	Definition
PC	Pancreatic cancer
Central and South-Central Appalachia	Individuals identified as living in this geographic region based on registry data (Eastern Kentucky, Western North Carolina, East and Central Tennessee, and South-West Virginia)
Tumor Registry	Central data collection source responsible for documenting and updating all cancer diagnoses and treatment courses for patients treated within a healthcare facility
Academic Medical Center	Teaching hospital with both clinical and research missions
GIS	geographical information service; spatial mapping software package
Access to care	Having a PCP, proximity to academic medical center
Stage	Measure of disease based on malignancy confined to its origin (Stage 0 – II), regional spread to surrounding structures/lymphatics (III), systemic spread (IV)
Overall survival	Categorical alive/dead; continuous: number of months survival from date of diagnosis

CHAPTER II THE FIRST ARTICLE & LITERATURE REVIEW

A version of this chapter was originally published by Andrew J. Ward: Ward, A. (2022). Pancreatic Cancer Risk and Screening Recommendations: Practice Impact. *Journal for Nurse Practitioners*, 18(5), 485–487. <https://doi.org/10.1016/j.nurpra.2022.02.012>

This article was the direct result and product of the graduate-level Nursing 610, State of the Science course. The final paper in this course was an integrative literature review. From this paper, I was able to create the published practice update for advanced practice nurses in primary and specialty care to increase awareness of pancreatic cancer. Evidence from all five themes identified in the original literature review is incorporated into the published article. This article was a solo effort on behalf of the author. No assistance in writing or editing this article was received. Supplementary materials curated for the comprehensive literature review including a PRISMA diagram outlining the literature review process and a literature review matrix of the reviewed articles are included with the appendix to this chapter.

Abstract

Pancreatic cancer is an aggressive disease with a poor prognosis. A prognosis is best when the disease is identified early. Nurse practitioners are well poised in their practice to recognize patients who may be at increased risk for pancreatic cancer based on previous medical history, family history of pancreatic cancer, or potential to have a hereditary predisposition to pancreatic cancer based on an inherited germline mutation. This review discusses the incidence of pancreatic cancer, the risk factors for pancreatic cancer, how to recognize familial risk, and which patients to refer for high-risk management.

Pancreatic Cancer Risk and Screening Recommendations: Practice Impact

Introduction

Pancreatic ductal adenocarcinoma (PDAC) has an abysmal prognosis and is the fourth leading cause of cancer death in the United States (Niederhuber et al., 2013). On a global scale, PDAC is the sixth leading cause of death, and resulted in 466,003 deaths in 2020 (Pancreas, 2020). Prognosis is best when patients are eligible for surgical resection. Unfortunately, by the time PDAC is diagnosed, only 15–20% of patients are candidates for pancreaticoduodenectomy or distal pancreatectomy (Niederhuber et al., 2013). For those patients who complete resection and have adjuvant systemic and radiation therapy, five-year survival is approximately 30% if there is no nodal involvement and only 10% when nodal involvement is present (Niederhuber et al., 2013). Thus, early identification of PDAC is a critical component to improving the prognosis of this disease. Nurse Practitioners (NPs) can play a vital role in this effort.

Prevalence

Annually, approximately 61,000 patients are expected to be diagnosed with PDAC in the United States (Siegel, 2021). PDAC often affects individuals after 45, but earlier diagnosis also occurs. Men are affected more than women (1.3:1), and Black Americans are more affected than White Americans

(McWilliams et al., 2018). Historically, PDAC is often identified too late for surgical intervention to be viable for patients who otherwise would tolerate resection. As a result, only a small portion of patients affected by PDAC will have a 10-30% survival prognosis in five years following diagnosis.

Risk factors for PDAC include modifiable environmental factors of tobacco use, obesity and physical inactivity, a diet high in saturated fats and processed meats, excess alcohol consumption, and diabetes mellitus with insulin resistance (Bosetti et al., 2012; Carreras-Torres et al., 2017). Hereditary factors also play a significant role, including a family history of PDAC and genetic predisposition syndromes (Grant et al., 2015; Shindo et al., 2017). NPs can play a role in identifying the risk associated with hereditary factors and genetic predisposition syndromes, whether they are in general or specialty practice.

Identification of PDAC

Early PDAC is often not associated with any specific clinical signs or symptoms. Instead, when patients present with symptoms, this is often in the advanced disease setting (Blackford et al., 2020). Signs and symptoms associated with PDAC include painless jaundice, hepatomegaly, cachexia, weight loss, epigastric pain, back pain, nausea and vomiting, diarrhea, and steatorrhea (Porta et al., 2005). An essential additional clinical sign includes the recent onset of diabetes mellitus (Batabyal et al., 2014). This is a key pearl for NP practice.

Initial evaluation of these symptoms often includes abdominal ultrasound, computed tomography (CT) imaging, endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography, and either percutaneous or endoscopic ultrasound guided (EUS) biopsy for tissue diagnosis. Often, this workup can be prolonged and delayed due to access issues to either specific services or specialty providers based upon geographic, financial, and healthcare navigation barriers (Lukács et al., 2019). NPs can play a vital role in recognizing signs and symptoms of PDAC early and facilitating timely and appropriate referrals to work up new cases of PDAC adequately. A thorough understanding of local referral resources, including gastroenterologists capable of performing EUS, is vital for prompt diagnosis.

Hereditary Risk Factors

Hereditary risk factors for PDAC include hereditary pancreatitis and a family history of two or more primary relatives with a diagnosis of PDAC (Klein et al., 2004; Tersmette et al., 2001). NPs providing care to individuals affected by chronic pancreatitis should recognize this as a risk factor for future PDAC, primarily when pancreatitis occurs chronically, in individuals with a family history of pancreatitis, and the absence of alcohol abuse (Rebours et al., 2012). Family history of PDAC can be recognized either through chart review or review of the

patient's family history in establishing with a new patient to the practice when eliciting the family history.

Acknowledgment of these risk factors is only the first step. Once recognized, these patients can then be referred to the appropriate providers to discuss pancreatic cancer screening. In most cases, this will be gastroenterology. However, in geographical settings where referral resources include tertiary academic medical centers with highly specialized providers, it may be possible to identify specialists who focus on these high-risk patients, e.g., oncology genetics, surgical oncology, high-risk, and survivorship clinics (Aslanian et al., 2020). In this case, an academic setting is the best choice for a referral because identified patients may be able to benefit from a broader selection of resources and even clinical trials unique to this group of patients. High-risk patients with a history of pancreatitis may have particular nutritional and metabolic needs that may best be served at specialty centers with greater access to resources (Arutla et al., 2021).

Genetic Predisposition Syndromes

Up to 20% of patients with PDAC have germline gene mutations implicated in their development of PDAC (Thompson et al., 2020). Germline mutations and genetic syndromes associated with an increased risk of PDAC include Hereditary Breast and Ovarian Cancer (HBOC) Syndrome BRCA1, BRCA2, and PALB2, Peutz Jeghers Syndrome (PJS) STK11, Familial Atypical

Multiple Mole and Melanoma Syndrome (FAMMMS) CDKN2A, Ataxia-Telangiectasia (AT) ATM, Familial Adenomatous Polyposis (FAP) APC, and Lynch Syndrome (LS) MLH1, MSH2, MSH6, and PMS2 (Thompson et al., 2020).

Identifying these mutations and their associated increased lifetime risk for PDAC has been well established (Hayashi et al., 2018; O'Neill et al., 2020; Young et al., 2018). Previous studies have also demonstrated the usefulness of point-of-care testing using multi-gene panel testing available through several commercial labs (Hayashi et al., 2018; Young et al., 2018). Not only can germline genetic testing help identify risk for PDAC, but in patients who are ultimately affected by the disease, genetic testing can also serve the purpose of helping to identify available treatment options (Golan et al., 2019; Javle et al., 2016; Sehdev et al., 2018). Germline genetic testing is well within the scope of NP practice, and there are specific training programs that NPs can take advantage of to incorporate this skill (King & Smith, 2020; Yoes & Thomas, 2020). The article from King and Smith (2020) provides an excellent review of resources for NPs interested in learning more about incorporating genetic risk assessment skills into their practice.

In addition to the determination of future cancer risk, it is important to consider the psychological impact of high-risk gene identification (O'Neill et al., 2020). Again, it is a role where NPs can actively support patients with PDAC risk and directly affect the quality of life. Assessing for and treating depression and anxiety associated with a PDAC diagnosis is a critical component of the palliative

and supportive care of PDAC patients that NPs are often engaged in (Védie & Neuzillet, 2019). Recent evidence suggests that sudden onset of depression or anxiety in an older adult may present as a precursor to disease, an especially concerning observation in those individuals who meet at-risk criteria based either on personal and family history or based upon having a known pathogenic variant associated with increased PDAC risk (Kenner, 2018). In individuals with a diagnosis of PDAC, referrals to Palliative Care should be considered early and even as soon as a diagnosis is made (Chung et al. 2021).

It is also essential to consider that PDAC screening should be considered in all individuals with the appropriate family history, not just individuals with a predominantly White ancestral background. As demonstrated in the introduction, Black Americans are disproportionately affected by PDAC, and early identification would significantly improve the overall prognosis for all population segments (McWilliams et al., 2018). Current literature does not accurately represent minority populations affected by PDAC, and here again, NPs can make a positive clinical impact. Offering genetic risk assessment and screening for PDAC, when clinically indicated, to all individuals is critical in improving the overall prognosis of this disease. NPs are often well positioned to provide this service to individuals who historically may not have access to genetic risk assessment and testing (Yoes & Thomas, 2020).

Recommendations

Surveillance for PDAC in patients with an identified high-risk includes using tools such as CT, EUS, MRI, and MRCP (Aslanian et al., 2020; DaVee et al., 2018). The frequency and when to begin surveillance are also well described (Aslanian et al., 2020; Verna et al., 2010). In general, surveillance starts after 50, and frequent surveillance is reserved for older individuals or individuals with abnormal findings. Current recommendations from the National Comprehensive Cancer Network (NCCN) are presented in Table 2. Similar recommendations are also provided by the (AGA). However, most gastroenterology and oncology practices will follow the guidelines set forth by NCCN (NCCN, 2021).

Individuals identified as high-risk for PDAC based upon genetic mutation should have referrals for genetic counseling. This should include the opportunity for cascade testing or testing of family members who may also be affected by the deleterious mutation and, therefore, at high-risk (Furniss et al., 2021). Genetic counselors may be available at academic centers and other high-volume oncology settings. However, accessibility is an issue. Again, NP's can provide the service of initial testing and subsequent cascade testing and provide access to genetic counselors (in person or via telehealth), improving the accessibility of this service through inter-disciplinary teamwork (King & Smith, 2020; Yoes & Thomas, 2020).

Conclusion

PDAC has a historically poor prognosis and is an example of how specific segments of the population have disproportionate access the healthcare services in the United States. This clinical feature demonstrates that early detection in PDAC can be improved by recognizing patients who may be at high-risk of developing this disease at some point in their lives. Increased awareness of PDAC risk for NP practice can contribute to improving prognosis. Additionally, genetic risk assessment goes in hand-in-hand with identifying PDAC risk, and this too is an essential skill that NPs can incorporate into their practice.

Many barriers that previously prevented some individuals, including minority patients, from participating in genetic risk assessment and testing can be solved by utilizing NP services, including physical and economic access barriers. NPs often practice in areas that serve medically disadvantaged patients, where specialty providers such as genetic counselors are not available. With appropriate training, NPs can fill this gap in care.

This clinical feature illuminates the efficacy and utility of genetic risk assessment and testing of PDAC-affected patients and their kindreds. Identifying at-risk individuals by screening programs can allow for high-risk surveillance that will ultimately lead to earlier identification of PDAC. Earlier identification ultimately improves prognosis. NPs are well poised to contribute to improving prognosis by increasing their awareness of PDAC and improving their ability to

recognize individuals with early symptoms or who may be at risk, and by incorporating genetic risk assessment skills into their practice when appropriate and when additional education and training are obtained.

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Appendix

Table 2 Pancreatic Screening Recommendations (adapted from NCCN Version 1.2022)

Indication for screening	Screening Recommendations
A known mutation and family history of PDAC in 1 first-degree or second-degree relative*	Screen with annual contrast-enhanced MRI/MRCP and/or EUS with shortening of intervals based on clinical judgment, findings present
<i>STK11</i> mutations	Beginning at age 30 – 35 (or 10 years before the diagnosis of the youngest family member with pancreatic cancer)
<i>CDKN2A</i> mutations	Beginning at age 40 (or 10 years before the diagnosis of the youngest family member with pancreatic cancer)
<i>ATM, BRCA1, BRCA2, MLH1, MSH2, MSH6, EPCAM, PALB2, TP53</i> mutations	Beginning at age 50 (or 10 years before the diagnosis of the youngest family member with pancreatic cancer)
Family history of PDAC in >2 first-degree relatives from the same side of family **	Beginning at age 50 (or 10 years before the diagnosis of the youngest family member with pancreatic cancer)
Family history of PDAC in >3 first/second-degree relatives from the same side of family**	Beginning at age 50 (or 10 years before the diagnosis of the youngest family member with pancreatic cancer)
Individuals with a known pathogenic variant in <i>PRSS1</i> and other pancreatitis genes and a clinical phenotype consistent with hereditary pancreatitis	Consider screening 20 years after the onset of pancreatitis, or age 40 (whichever is earlier)

Note: Recommendations from NCCN include screening to be performed in appropriate centers. High-risk patients should have access to appropriate providers to discuss the benefit (known and unknown) of pancreatic cancer screening.

* From the same side of the family as a pathogenic variant

** with or without a known pathogenic variant

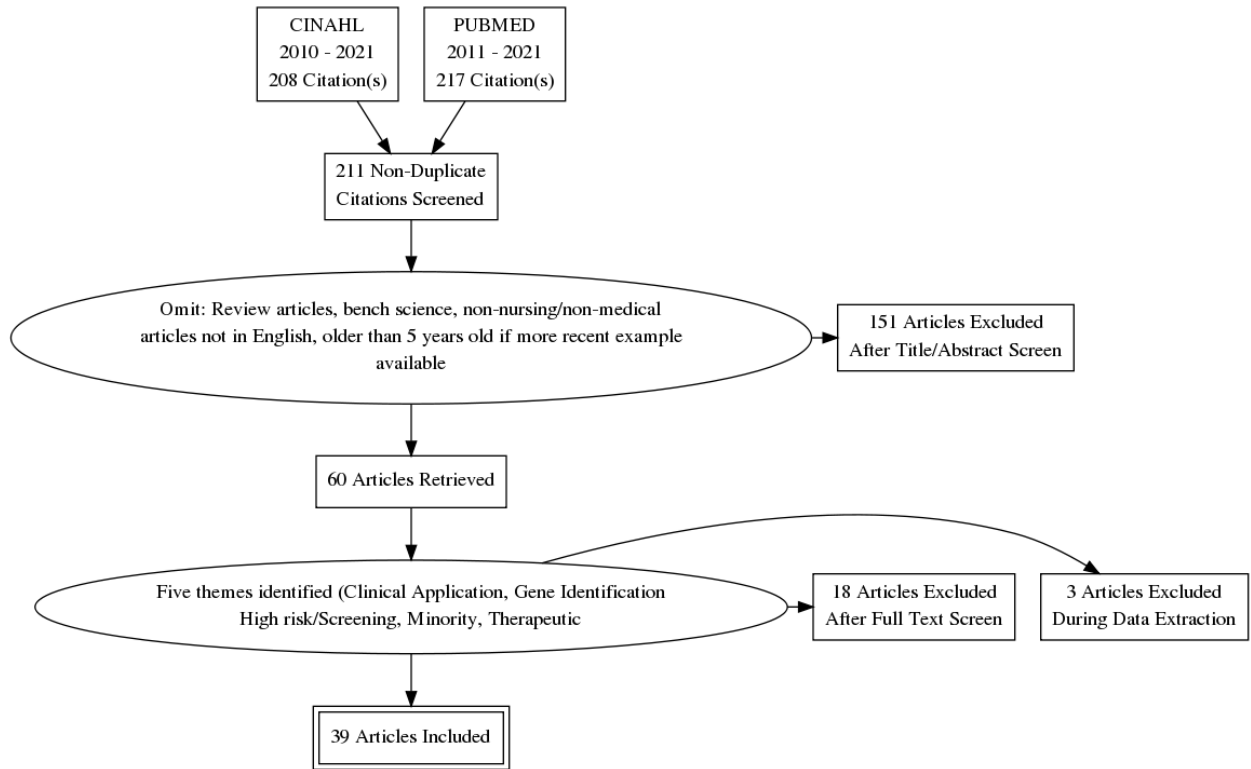


Figure 1 PRISMA from Integrative Review of Genomics in Pancreatic Cancer

Note, PRISMA diagram of literature review process obtaining data from electronic databases.

Search terms included “pancreatic cancer,” “genetics,” “germline mutations,” and “hereditary risk.”

This search was limited to articles published within the last ten years.

Table 3 Literature Review Matrix – Germline Genetic Application to High-Risk Screening and Management in Pancreatic Cancer

Clinical Application

Author/ Date	Theoretical/ Conceptual Framework – Discipline Source	Research Question(s)/ Hypotheses	Methodology/Study sample and sample characteristics	Analysis & Results/Finding s	Conclusions/ Discussion	Study limitations and strengths	Next steps for me to consider
Hayashi et al 2018	Medicine, Oncology	Not explicitly stated. What is the clinical utility of genomic testing for patients with PDAC?	Retrospective analysis of a convenience sample taken from the study institution. Somatic testing performed on all individuals sampled. Germline testing only conducted if secondary findings identified on somatic, and then agreed to by patient. ONLY pathogenic findings disclosed (No VUS???)	All patients had PDAC (resected or not), ECOG status of either 0 or 1 (see p 648 results description for their rationale); 17 pts w family hx of some type of cancer, 3 with PDAC. 18/20 had received chemo, DNA collected from archived tissue in 15/20 pts. 5 required repeat bx. Actionable gene alterations (somatic) in 100% of pts.	Successful genomic testing is possible in PDAC pts and can identify druggable gene alterations when focused on appropriate genes. This can help direct systemic therapy to what would be most effective to the individual patient (traditional systemic chemo, PARP, immunotherapy)	This paper is primarily focused on the somatic genetic findings and may have missed true germline mutations based on study design.	Univers al testing (germlin e and somatic) for personal ized medicin e

Table 3. Continued Clinical Application

Greer et al 2009	Medicine	How can clinicians best recognize hereditary forms of pancreatic cancer	Literature review divided into sections by hereditary pancreatitis, cystic fibrosis, and then genetic syndromes (Peutz Jeghers, Familial atypical multiple mole melanoma, <i>BRCA1/2</i> , Lynch, FAP	Hereditary pancreatic cancer is complex and represented pathology. In order to improve prognosis, providers need to improve ability to recognize hereditary PDAC so that PDAC can be identified as early as possible. This includes high-risk screening, and accounting for other factors such as smoking which can result in a 10 year earlier onset.	Better identification of at risk = high-risk screening = earlier detection = (ultimately) decreased mortality -- Need access to high-risk screening modalities (EUS). When to intervene based on screening findings controversial due to morbidity a/w pancreatectomy. Genetic counselling of high-risk pts critical.	One study found that a “do nothing” approach yielded the best outcome. Existing studies are small, larger studies needed to know true incidence. Not one size fits all. More penetrant mutations may require more aggressive screening/prophylaxis	Larger studies, population specific studies, biomarker?
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Table 3. Continued Clinical Application

Young et al 2018	Medicine, oncology	What is the best approach to provide genetic risk assessment to individuals at risk to hereditary malignancy? Can PDAC serve as a "sentinel?"	Convenience sample of 274 cancer patients at study institution, unselected for family history and meta-analysis including published panel tests of unselected PDAC. All pts PDAC. Initial study group 34 gene panel, subsequent 59 gene panel and then last with 14 gene panel.	Statistical analysis (random effects model, Freeman-Tukey transformation to stabilize variances between studies, estimated Standardized Incidence Ratios (SIR), Poisson distribution to test sig of confidence intervals, genes split into sub-groups of high and moderate penetrance). Summary of findings from each study in meta-analysis. Carrier frequency of 8.6% calculated from analysis. Assess if patients would have met NCCN criteria for genetic eval (based on dx, PMH and FH) -> 23% of identified carriers WOULD NOT HAVE MET criteria.	Estimate that hereditary risk for pancreatic cancer a/w 2.7% HBOC genes, 1.3% Lynch, and 5.1% other (Li Fraumeni, Familial Melanoma Syndrome, and individuals' genes). Precedent for universal testing comes from universal CRC testing. Testing based on clinical guidelines results in delay and ~50% loss in f/u. Targeted therapies on the horizon (now available since publication) as options for systemic tx when first- and second-line therapies fail	Variation in gene panel by study (missed opportunity in smaller panels?), overall small samples. Samples are not heterogenous .	Larger scale study with broad germline panels, collaborative studies with open access to reduce access to care obstacle , remote studies from centralized locations so increase participation and equal access
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Table 3. Continued Clinical Application

Catts et al. 2016	Medicine, genetics	Can state-wide high-risk cancer registry help identify families at a high-risk for pancreatic cancer?	GC population cancer registry data on all patients seen through cancer center in Delaware. This data is used to examine pedigrees and identify hereditary patterns of cancer	Descriptive study, sample size of 4567 from cancer registry, 597 had pedigree matches (family member with PDAC 1,2,3 degree), attrition of all but 175 families. 52/175 (29.7%) germline mutation (<i>BRCA</i> ½, <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>ATM</i> , <i>CHEK2</i> , <i>TP53</i> , <i>RAD51D</i>).	Only 54 of the 175 families met familial pancreatic cancer criteria. 106 of 175 considered first degree families. 23 affected probands pursued genetic testing with 13/23 having <i>BRCA1</i> or 2 mutations. PDAC is lethal and complete surgical resection is the only curative option. Many patients identified too late and improving screening of high-risk pts by identifying these pts early and offering screening is key to improving prognosis	Excellent tables outlining identified germline mutation genes and frequency of those gene mutations. Limitation Cannot be generalized to PDAC as most of those tested were tested for diagnoses other than PDAC Pts were tested based on recs by GCs from guidelines only, panel testing cost-prohibitive at time of study. (No longer the case with NGS)	Repeat study on a larger sample of pts from registry data and “biobanks” where PMH and FH are known factors with NGS testing (larger, more comprehensive panels)
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Table 3. Continued Clinical Application

Maker et al. 2009	Medicine, surgery	Case study only, OMIT from further review		Germline mutation in p16 a/w FAMMM-PC (familial atypical multiple mole melanoma – pancreatic cancer syndrome)			
O'Neill et al. 2020	Medicine	Great intro framing the potential future dilemma: other malignancies are improving in prognosis while PDAC is worsening due to no systematic screening method Discussion of screening methods Determine the short- and long-term psychological impact of screening in participants in prospective PDAC	Prospective analysis of questions designed to assess psych impact of PC screening Participants identified by being involved in study on PDAC screening. IRB approved Referred by providers or self-referred, initial screening by mail, screening tools for distress were specific to the population	Basic statistical analysis performed with SPSS, well described and could be easily repeated. Some detail missing. Results were interpreted based on demographic and medical differences between study participants.	No negative psychological side effects in the short- or long-term study participants. At one year, there was a decrease in IES scores and those who had an abnormal screening EUS were positively impacted by the program. Those who participated who had the greatest distress at the beginning had a significant reduction in their overall levels of distress at both study measurement intervals. Those with a personal history of malignancy had greater worry scores.	Limitation: screening by mail would result in a high attrition rate I would imagine (only ~50% of individuals identified as at risk participated in study.) Statistical analysis description failed to mention why data were not normally distributed	This study was conducted in an environment that was conducive to such a study. It would be interesting to see if the findings would be replicated in our health care system where high-risk PDAC is not considered standard of care and often takes place

Table 3. Continued Clinical Application

Aspinwall et al. 2013	Psychology	Examine short and long-term impact of <i>p16</i> counseling and testing on psychological outcomes (anxiety, depression, worry about melanoma and pancreatic cancer among affected and unaffected carriers and affected and unaffected non-carriers)	IRB approved Study participants drawn from at least two prior studies (FH and PMH known). Comprehensive phenotyping and mutation testing for <i>p16</i>, results NOT disclosed to pts. Primary concern was hereditary risk for melanoma, PDAC was secondary. 77 subjects identified based on criteria, and 53 enrolled. Hospital Anxiety and Depression Scale (HADS) at 1 month, 6 months, 1 year and 2 years Multidimensional Impact of Cancer Risk Assessment (MICRA) at 1 and 6 months.	ANOVAs testing change in anxiety, depression and melanoma worry as a fx of time assessment (baseline, 1 month, 6 months, 1 year, and 2 years). Repeated measures ANOVA tested worry about PDAC as a function of time assessment. Repeated measures ANOVA tested whether the groups reported significant differences in test-related distress, uncertainty, or positive experience. HADS = Low levels of depressive sx across study. All groups reported decreased anxiety over the study period. PDAC worry was low for all groups. MICRA results, affected carriers (<i>p16</i> mutation) reported the greater levels of distress and uncertainty. -unaffected carriers reported favorable experience	No evidence of short- or long-term increase in anxiety, depression, worry about melanoma or pancreatic cancer after receipt of <i>p16</i> mutation results. Qualitative reports of costs and benefits of genetic testing -> all participants able to verbalize at least one perceived benefit (emotional, informational, behavioral) one only one reporting a cost (not being able to change their mutation)	Inconsistent participation over the study period with completing questionnaires Homogenous population not representative of US pop as a whole Well-designed table/figure describing results	Larger application of the study, application to panel testing, application to VUS results, application in affected populations with negative NGS results
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Table 3. Continued Gene Identification

Author/ Date	Theoretical/ Conceptual Framework	Research Question(s)/ Hypotheses	Methodology/S tudy sample and sample characteristics	Analysis & Results/Finding s	Conclusions/ Discussion	Study limitations and strengths	Next steps for me to consider
Roberts & Klein 2013	Medicine, Epidemiology Historical context, foundational for NGS testing and multigene panels. Cost improvement	1. discuss use of genome wide sequencing to id genetic basis of disease and cancer syndromes 2.outline current knowledge of genetic basis for hereditary PDAC 3. highlight challenges to ID PDAC susceptibility genes	Lit review	Lit review on each of the article goals	Summary of the current lit (currently much outdated)	Dated	Done by other articles

Table 3. Continued Gene Identification

Hu et al. 2015	Medicine	Implication of panel screening on identification of PDAC susceptibility genes to determine important ramifications for patients and family members	Pts identified with PDAC within MAYO system. Recruited over one year. Germline testing (DNA).	X^2 , t test and fisher exact test for association studies. Homogenous study (97% Caucasian), no Ashkenazi Jewish inclusion. -14/96 mutations identified. Carriers had a significant family hx of breast cancer, pancreatic cancer, (colorectal/endo metrial) in 1 st degree relatives. No significant a/w personal hx malignancy	These findings contrast with a similar study conducted in Ontario with a higher number of germline mutations identified (9.4% compared to 3.8%), partially explained by the panel testing approach including greater numbers of genes. <i>BRCA2</i> is an important PDAC predictor gene. MMR genes (<i>MLH</i> , <i>MSH2</i> , <i>MSH6</i> and <i>PMS2</i>) also a/w increased PDAC risk	Greatest limitation here is time. At the time of publication, a 14 gene panel was a large panel. We can now easily order gene panels with excess of 87 genes	Apply same study initially to a small group at a single high-volume center for PDAC and then broad application to multiple centers. Effort to reflect greater diversity of PDAC patients
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Table 3. Continued Gene Identification

Lucas et al. 2013	Medicine	<i>BRCA1</i> and <i>BRCA2</i> play a significant role in the pathogenesis of hereditary PDAC through loss of heterozygosity. Assess prevalence of <i>BRCA1/2</i> mutations in an Ashkenazi Jewish cohort and determine if LOH present.	All pts underwent surgical resection for pancreatic disease at Columbia Medical between 2003 and 2011 and frozen tissue from these individuals was analyzed.	63 patients of Ashkenazi heritage were sampled. These represented pts who had pancreatic surgery, not just PDAC but also benign lesions and PNET. <i>BRCA1</i> and 2, 12 of 63 (19%) carried founder mutation in <i>BRCA 1</i> or 2. LOH was found in 2 of the 4 <i>BRCA1</i> associated PDAC, and 3 of 4 <i>BRCA2</i> associated PDAC. Mean age of dx of PDAC in <i>BRCA1</i> or 2 carriers was 63.8 yrs compared to 70.0 in non-carriers.	This article demonstrates that <i>BRCA 1</i> and 2 carriers presenting to breast cancer prevention clinics had an infrequent family hx of PDAC compared to carriers who present to PDAC genetics and prevention programs. Suggests not all <i>BRCA</i> mutations are the same or convey the same risk of malignancy.	Limited to the population it is examining, study states this and 1 Study included multiple diagnoses, not just PDAC Study limited to <i>BRCA 1</i> and 2 founder mutations in this population. Other mutations may have been overlooked	1 a future direction would be to apply the same study to other populations to identify their “founder mutations” and differentiate risk for malignancy depending on mutation
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Table 3. Continued Gene Identification

Iqbal et al. 2012	Genetics, medicine, public health	What is the incidence of PDAC in a cohort of <i>BRCA</i> 1 and 2 carriers	Prospective study, sample of 5149 women with known mutations. Excluded women w a hx of ovarian ca. Following attrition, sample of 5089 women. Women were followed via questionnaire until a. dx of PDAC, b. dx ovarian ca or c. death.	Risk was calculated in the study group using standardized incidence ratios (SIRs) and SIRs were also calculated for each participating country represented. SIRs were also estimated for each age group. Women in study group were followed for a mean of 1.95 yrs. 8 new PDAC were identified versus the expected 3.28 (SIR = 2.44, p = 0.03) 6 occurred in <i>BRCA</i> 1 and 2 in <i>BRCA</i> 2 carriers. All in women > 50 yrs. 2 of the women had a first degree relative with PDAC.	2.4-fold increase in the incidence in PDAC in female <i>BRCA</i> carriers. Greatest risk > 50 yrs old. 5-year survival = 6%.	Limited to female patients only.	Repeat with men included.
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Table 3. Continued Gene Identification

Lucas et al. 2014	medicine	Create evidence-based guidelines for PDAC screening in <i>BRCA</i> mutation carriers	All pts referred to the pancreas cancer prevention and genetics program included (2005 – 2011). Demographics and genetic risk assessment and testing performed. Additional patients referred based on genetic testing results finding mutation status. Additional 17 pts referred after dx of PDAC.	Pts with no prior PDAC stratified into average, moderate, and high-risk categories. See highlighted areas in article for definition of average, moderate, and high-risk as well as what screening involved for each group	37 pts engaged in screening. All were Caucasian, 86.5% were Ashkenazi Jewish ancestry. 6 of the AJ were found to have founder mutations and one <i>BRCA2</i> mutation found in a non-AJ pt. (7/37 or 18.9%). Of the 20 known genetic mutation carriers referred, 95% were Caucasian, and 80% were AJ. 10 of the AJ had founder mutations, 3 had non founder <i>BRCA2</i> mutations and the remaining 7 did not in fact have a mutation. Screening results high diagnostic yield of 18.9% and 21.8% in <i>BRCA1</i> and 2 pts bzw.	If Ashkenazi pts were only tested for founder mutations as is implied on p 1961, this may have missed mutations! Methods and results are whitening in a very confusing way with too many subgroups. May have been more valuable to split this into more than one article. Pts represented had greater than average risk based on sample selection. Majority of pts AJ.	Apply to more broad pop
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Table 3. Continued Gene Identification

Salo-Mullen et al. 2015	Medicine, genetics	Determine prevalence of germline mutations in consecutive series of patients with PDAC seen in the clinical genetics service at MSKCC.	Retrospective review of pts seen from 2011 – 2014 including all PMH, FH, and genetic testing results. Looked at <i>BRCA1/2</i> and Lynch, <i>PALB2</i> and FAMMM genes. Statistical analysis using chi-squared test.	175 pts identified. FH of cancer (breast, pancreatic, colorectal, & ovarian). Based on guidelines, 166/175 pts offered testing with 159 tested. Germline mutations identified in 24/159 (15.1%) w prevalence in early onset PDAC of 28.6% (prior to age50)	One of the largest scope studies to date (of pub). <i>BRCA2</i> most common gene a/w PDAC. Study represents one of the largest cohorts of AJ pts.	Selection bias (pts were referred for GRA and testing for PDAC). Possibility of missed mutations due to pts not testing. Homogenous pop, no minority representation.	Broader scope study, all backgrounds with effort to include minority PDAC pts.
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Table 3. Continued Gene Identification

Ghiorzo et al. 2012	Medicine, genetics	Provide the first assessment of germline mutation frequency in <i>BRCA1</i> , <i>BRCA2</i> and <i>PALB2</i> in Italian PDAC pts selected according to their personal hx and FH.	Pedigree review on 225 known PDAC pts from 1999 -2011 from a previous ongoing case-control study on the genetics of PDAC. Pts gave consent and blood was donated with pedigree info via questionnaire including FH of cancer. Diagnoses of cancer were confirmed in medical records. Pts were considered eligible for germline testing if 2 or more family members with PDAC, BC or OC (at least one a first degree relative), a PDAC case w at least one relative with BC	4 <i>BRCA1</i> mutations. Based on the Guidelines at the time of pub, 9 of 29 pts met criteria for testing. 3/4 were +. 3 <i>BRCA2</i> mutations were identified. No <i>PALB2</i> mutations. Total mutational frequency 7/29 (24.1%)	Of the 9 families who met criteria for testing, 3 were +. Of the remaining 20, 4 were +. Strict following of guidelines likely underrepresents affected individuals (carriers)	Small sample size, small panel of genes reviewed. Presentation of results confusing, somewhat illogical.	Expand study to include all known individuals w PDAC and larger panels
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Table 3. Continued Gene Identification

Zhen et al. 2015	Medicine	To better inform genetic counseling of patients and families through more precise prevalence estimates large scale testing of <i>BRCA1</i> , 2, <i>PALB2</i> and <i>CDKN2A</i> in a large cohort of familial PDAC kindreds.	Multicenter prospective trial w 2853 familial PDAC kindreds (unrelated with at least two family members affected by PDAC. A total of 727 participated in study, 521 fully met criteria	Sample was largely Caucasian (87.3%), 43 (8%) were of AK descent. 4 novel <i>BRCA2</i> mutations were identified, total germline mutation = 48 (6.7%) VUS total 35 (4.9%) – 8% of those with mutations did have hx consistent with familial PDAC	Mutations in <i>BRCA2</i> and <i>CDKN2A</i> were found more often than <i>BRCA1</i> or <i>PALB2</i> consistent with prior studies. FH of BC, OC, or melanoma, pt has an 8.7% probability of carrying a germline mutation. Study confirms the heterogeneity of PDAC, if genetic testing is performed results support mutli-gene testing. Previous studies emphasized importance of FH, but this study suggests more relaxed criteria to ensure all high-risk pts identified	Lack of diversity, overall small number of genes studied (study reflects fast paced changes in genetics and NGS testing)	Repeat on larger scale with attempt to include more diverse pt pop, larger gene panels. Combine with somatic testing
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Table 3. Continued Gene Identification

Hu et al.	Medicine	To determine whether inherited germline mutations in cancer predisposition genes are a/w increased risks of PDAC	Case-control analysis to identify PDAC predisposition genes, longitudinal analysis of PDAC pts for prognosis. 3030 adults with PDAC enrolled in Mayo registry from 2000 – 2016 w last known f/u 2017. Reference controls from 123126 pts with exome sequencing data in the public GAD and 53105 from the EAC database	Germline mutations from 21 cancer predisposition genes identified and assed.	Sig a/w <i>CDKN2A</i> , <i>MLH1</i> , <i>BRCA2</i> , <i>ATM</i> , <i>BRCA1</i>	The six genes identified were responsible for 5.5% of the PDAC, and 7.9% of the pts with a sig FH of PDAC – those with mutations had an earlier onset compared to non-carriers (62.5 vs 65.3), esp. in <i>BRCA2</i>	Wider study, more diverse pop (95.6% non-Hispanic/white)
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Table 3. Continued Gene Identification

Kastrionos et al. 2009	Medicine, genetics	To estimate PDAC risk in families with germline MMR mutations	Cancer registry data reviewed from Dana Farber and from Michigan (n = 80, n = 67). Age-specific cumulative risks and hazard ratio estimates of PDAC calculated and compared to gen pop using modified segregation analysis w correction for ascertainment	Data from 6342 pts from 147 families with known MMR mutations analyzed. 31 families (21.1%) reported at least 1 PDAC. 47 PDAC reported. Cum risk for PDAC 1.3% up to 50 yo, and 3.68% up to age 70. This represents an 8.6-fold increased risk compared to gen pop.	Individuals with MMR mutations are appropriate to consider for high-risk screening.	To account for ascertain bias, families with known classic lynch tumors (colorectal, endometrial, sebaceous carcinoma) were excluded. This may have missed PDAC pts. Some family members may have been missed due to incomplete pedigrees. Homogenous pop (? Don't know, this info isn't disclosed)	Broader study to include more diverse population, include affected individuals and their families
Rizzaot et al. 2011	Medicine, genetics, public health	Replication study of previous work to see if previously identified mutation implicated in an independent sample of PDAC pts	Multi-center, mutli-national study collection samples from pts from 1996 – 2009.	Looking at SNPs a/w possible genetic pre-disposition. Not a germline study			

Table 3. Continued Gene Identification

Wei et al. 2012	Public health, medicine	NOT GERMLINE - OMIT					
Blanco et al. 2013	Genetics, medicine, public health	Determine the prevalence of <i>PALB2</i> mutation in a population of <i>BRCA1/BRCA2</i> negative breast cancer patients selected from either personal or FH of known PDAC	132 non-BRCA breast/OC families selected. <i>PALB2</i> analysis performed by direct sequencing	Two <i>PALB2</i> (2/132, 1.5%) identified – several VUS of <i>PALB2</i> detected	Prevalence of <i>PALB2</i> in hereditary PDAC is similar to other research studies	Strength, pop all Spanish heredity, previously not represented well in lit/studies	Broader inclusion criteria, larger panel testing now that less expensive with NGS sequencing
Yurgelun 2019		Determine prevalence of germline cancer susceptibility gene variants in PDAC paired with somatic and survival analysis	Germline and somatic DNA analyzed from 289 known PDAC pts, All variants assessed for pathogenicity, outcomes analyzed using multivariable-adjusted Cox proportional hazard regression	28/289 (9.7%) carried pathogenic germline mutations. Somatic sequencing identified “second hits” on the tumor in 12/27 (44.4% of pts with germline variants – 1 failed sequencing). Compared with noncarriers	10% of pts with PDAC had germline variants, majority lack “second hit”	Small study, better diversity	Suggest similar study prospectively in multiple centers to increase number of subjects, idea of current somatic testing is interesting, but how valuable to translational

Table 3. Continue Gene Identification

Leof et al. 2019	Public health, medicine	Assess if pts with <i>CDKN2A</i> mutations would f/u with recommended screenings for melanoma and PDAC	Selected from the pancreatic research registry, 133 total. Perceived risks, screening intention and behavior assessed pre- disclosure of result and 6 months post- disclosure	80 agreed to participate and 63 completed study. 73% of the carriers and 47.5% of the non- carriers intended to participate in confirmatory testing, 20%/2% followed through. All shared results with family.	Recipients of cancer genetic risk results may not follow through with recommended screenings. Carriers were more motivated than non-carriers	Small sample, short interval of study	Larger sample, incentivized, look beyond <i>CDKN2A</i> but all PDAC risk
Yang et al 2016	Public health, genetics, medicine	Expanded germline testing performed on PDAC pts with <i>CDKN2A</i> mutations. Also evaluated pts w/o <i>CDKN2A</i> mutations but a family history of PDAC and melanoma.	66 pts included in analysis.	35 rare variants found in 15 genes.	Pts with MMR gene mutations had a more significant risk/burden of disease. Role of FH inconclusive. Hx or FH of digestive organ malignancies increase risk.	Small study	

Table 3. Continued High-risk screening/Early Detection

Author/ Date	Theoretical/ Conceptual Framework	Research Question(s)/ Hypotheses	Methodology/Study sample and sample characteristics	Analysis & Results/Findings	Conclusions/ Discussion	Study limitations and strengths	Next steps for me to consider
Aslanian et al. 2020	Medicine	Describe indications for screening for PDAC in high- risk individuals	Evidence reviewed from reports on screening studies for PDAC of high-risk individuals and expert opinion	PDAC screening in high-risk individuals with a first degree relative with PDAC, and at least two affected relatives.2. PDAC screening in individuals with genetic syndromes associated w increased risk of PDAC.3. GRA and testing for familial cancer relatives eligible for surveillance. 4.Particpatipation in a registry or referral to a pancreas center of excellence should be pursued for high-risk individuals.5. Clinicians should NOT screen average risk individuals. 6. Screening should begin at 50, or 10 years younger than the initial age of familial consult. 7. MRI and EUS should be used in combination. 8. Target detectable lesions are stage I PDAC, IPMN		None!	This is excellent, must up to date recommenda- tion that I have seen.

Table 3. Continued High-risk screening/Early Detection

DaVee et al. 2017	Medicine, public health	Assess the yield of PDAC screening in patients with high-risk mutations	Asymptomatic, high-risk pts underwent screening w EUS, MRI or CT during a 10 yr. period and were retrospectively reviewed. High-risk carrier of <i>BCRA1</i> , <i>BRCA2</i> , <i>TP53</i> , <i>STK11</i> , <i>MSH2</i> , <i>ATM</i> , <i>APC</i> . Pts that were non-carriers were excluded.	86 pts met criteria, screening detected abnormality in 26.7% (cysts, hyperechoic strands and foci, mild ductal dilatation. Pt older than 60 were more likely to have PDAC detected. EUS detected more PDAC than MRI or CT. No cases of PDAC were detected.	Unless otherwise indicated, screening younger than 50 not indicated. Annual EUS may be sufficient.	Limited b/c it was retrospective. Equipment updates occurred during the study. Study was not very diverse (77.9% European ancestry)	Expand to larger study, multiple centers, increase diversity
Underhill et al. 2015	Medicine, public health, NURSING, phenomenological study	Understand the meaning and experience of living with familial PDAC risk and explore experiences related to screening and prevention	Participants underwent semi-structured interviews. Pts w/o PDAC who met familial or hereditary risk criteria were eligible. Thematic analysis of transcripts performed to id patterns, consistencies, and differences. Compared to existent lit of women	19 participants (9 male, 10 female). Themes include experience w PDAC, and PDAC death and associated grief. These experiences affected how individuals perceived and approached their own risks. Participants wanted to control	Begin to describe how an individual approaches, perceives their own risk to PDAC. PDAC risk may differentiate from other hereditary risk syndromes because of how lethal PDAC is.	Small study, specific to study pop	Great start, now EXPAND!

Table 3. Continued High-risk screening/Early Detection

Saldia et al. 2019	Public health, medicine	In healthy individuals with high-risk, do individuals with <i>BRCA1</i> or 2 mutations have a higher risk than those who do not have <i>BRCA1</i> or 2 mutations?	Registry study, relatives of patients with PDAC. Each pt interviewed and completed a detailed questionnaire. PMH, SH and FH data collected. Annual surveillance with MRCP/CT. Data analyzed by total and by group (carrier vs non-carrier). Logistical regression used to estimate outcome ratios and to eval influence of mutation status and characteristics a/w presence of IPMN.	75% participants were women. 93% white. 54% had AJ grandparents. Those with a path mutation were more likely to be AJ. Most AJ mutations were founder mutations. Median length of surveillance was 60 months with a range of 0-127.	35% were found to have an abnormality on MRCP/CT. 27 of 29 were found to be IPMN. Two additional findings, pancreatitis and a met of serous Mullerian malignancy. Surgery was indicated in 4 pts, 3 w IPMN and 1 w malignancy.	No difference was found between the two groups.	Larger pop study with more diversity. Look also at other genes implicated in PDAC
Verna et al. 2010	Medicine	Is screening effective in patients identified as high-risk for PDAC?	Previously identified high-risk pts enrolled in screening using EUS and MRI.	51 pts in 43 families enrolled. 13 underwent EUS and 33 MRI. EUS identified 2 PDAC, 5 IPRM, seven w cysts or parenchymal changes. 24 of 53 (47%) had genetic testing.	Screening in pts at high-risk (family hx, PMH and/or germline carrier status) is effective at identifying asymptomatic malignancies.	Small study, not diverse.	Expand, larger scale and more diverse population.

Table 3. Continued High-risk screening/Early Detection

Klein 2013	Medicine	Are family registries useful in the study of PDAC, and what opportunities for research develop from these registries?	Lit review of registry data	Useful for: family aggregation, risk quantification using family history data, genetic risk factor identification, environmental risk factor identification, gene discovery, risk model development/validation, early detection tools and trials, personalized therapy,		Powerful tools, diverse usefulness	Periodic update of available registries for public research?
Ohmoto et al. 2019	Genomics, medicine	Present an overview of current PDAC associated syndromes, and describe current status and future prospects of surveillance programs and therapeutic	Review of PDAC associated syndromes *Peutz-Jeghers Syndrome, hereditary pancreatitis, Familial Atypical Multiple Mole Melanoma, Familial Adenomatous Polyposis, Lynch Syndrome, Hereditary Breast and Ovarian Cancer Syndrome.	Germline mutation prevalence vs. sporadic pancreatic cancer (range of germline is 2.6 – 14.5%) whereas sporadic incidence is (NOT ACTUALLY LISTED!), Many of those identified as germline carriers in studies reviewed would have been missed	Identification of high-risk mutations should be followed by high-risk screening and in individuals with PDAC PARP inhibition therapy, possible immunotherapy benefits	Small study, limited to Japanese population, however, fills a gap in existent lit as not well represented previously.	Broader application, periodic updates due to dynamic nature of genomics, precision medicine, immunotherapy

Table 3. Continued High-risk screening/Early Detection

Ghiorzo 2014	Medicine	Update to genetic susceptibility in PDAC as well as data from an Italian pop				No additional contributions not covered by other articles, dated	
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Table 3. Minority

Author/ Date	Theoretical/ Conceptual Framework	Research Question(s)/ Hypotheses	Methodology/Study sample and sample characteristics	Analysis & Results/Findings	Conclusions/ Discussion	Study limitations and strengths	Next steps for me to consider
McWilliams et al. 2018	Medicine public health, genetics	Examination of the role of <i>CDKN2A</i> on this risk of PDAC in minority groups	<i>CDKN2A</i> sequenced in 220 African Americans with PDAC with ~900 AA controls and 183 Nigerian controls. Frequencies determined for each group, Odds ratios and 95% confidence interval calculated for case-by-case comparison. Small sets of Hispanic and Native American samples also obtained	A novel missense mutation was identified, and a novel frameshift mutation was identified. Carrier status a/w increased risk for PDAC compared to control groups. AA pts had a higher frequency of rare variants as compared to the non-Hispanic white population.	This research suggests an increased effort in identifying hereditary risk in AA and other minority populations would be fruitful	Small size, small size of minority groups that are non-AA	Expand!

Table 3. Continued Minority

Tavakkoli et al. 2020	Medicine	Characterize racial disparities in PDAC incidence, mortality, time periods, age groups, and disease stages/	Descriptive study. NOT GERMLINE but provides excellent foundation for need and identified GAP IN THE LIT				
Siegel et al. 2020	Public health	Descriptive study/ state of oncology/cancer in the US.	Foundational information. NOT GERMLINE				
Nipp et al. 2017	Medicine	Assess whether survival and treatment disparities exist after adjusting for demographic and clinical characteristics	Foundational, NOT GERMLINE				
Stadler et al. 2012	Medicine	Clinical database review of <i>BRCA1</i> and <i>BRCA 2</i> mutations in Ashkenazi Jewish families with history of breast and pancreatic cancer	Foundational				

Table 3. Continued Therapeutic Applications

Author/ Date	Theoretical/ Conceptual Framework	Research Question(s)/ Hypotheses	Methodology/Study sample and sample characteristics	Analysis & Results/Findings	Conclusions/ Discussion	Study limitations and strengths	Next steps for me to consider
Shi et al. 2017	Medicine	Summary of current regimens for chemotherapy for advance PDAC and highlight combo of chemo and targeted therapies tested in recent trials	Lit and guideline review		No GERMLINE discussion, all are somatic mutation targets		
Javle et al 2016	Medicine	Translational use update, review current status of stromal, KRAS and immune targeted therapeutic approaches for PDAC a/w DNA repair mutations	Lit review	Overview of PARP use in <i>BRCA</i> carriers (<i>BRCA1</i> , <i>BRCA2</i> , <i>PALB2</i>)	Potential for <i>ATM</i> to be a target as well	Lit review, dated, need broader trials	

Table 3. Continued Therapeutic Applications

Sehdev et al. 2018	Medicine, public health	Assess DNA damage repair (DDR) gene mutations as a predictive biomarker in PDAC patients treated with FOLFIRINOX	Participants selected from clinic population, PDAC dx, FOLFIRINOX tx first line, available tissue Descriptive stats to summarize baseline characteristics and mutations in DDR genes (<i>BRCA1</i> , <i>BRCA2</i> , <i>PALB2</i> , <i>CHEK1</i> , <i>CHEK2</i> , <i>RAD51</i> , <i>MLH1</i> , <i>MSH2</i> , <i>ERCC1</i> , <i>ERCC4</i> , <i>PARP1</i> , <i>FANCF</i> , <i>ATR</i> , <i>MDC1</i>) and cohort divided into those with germline and somatic mutations and those w/out using chi squared analysis and students t. Also conducted a time to event (death or last f/u) analysis using Kaplan Meier curves to estimate overall survival (OS) Conducted sensitivity analysis looking at <i>BRCA1</i> and <i>2</i> status.	47 pts in cohort. 11 excluded (inability to locate tissue or low cellularity). 36 pts in final cohort. DDR mutations found in 12/36 (33.3%). Pts with DDR mutations had the highest OS and specifically those with <i>BRCA1</i> and <i>BRCA2</i> .	Assessment of DDR mutation status can aid in treatment selection, estimation of prognosis in PDAC patients.	Small study, not diverse	Expand, mutli-center, increase minority representation
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Table 3. Continued Therapeutic Applications

Golan et al. 2019	Medicine	Randomized, double-blind, placebo-controlled phase 3 trial to evaluate efficacy of PARP inhibitor as maintenance therapy in patients with germline <i>BRCA1</i> and <i>BRCA2</i> mutations with PDAC who had NOT PROGRESSED during first line therapy with platinum-based agents. End point was progression free survival (PFS).	154 pts participated, 92 received PARP inhibition, 62 placebo).	Median PFS was significantly longer in treatment group vs placebo group (7.4 months vs. 3.8 months p = 0.004). No difference in OVERALL SURVIVAL OS), 18.9 vs 18.1 months, p = 0.68). No significant difference in quality of life (QOL) based on QOL questionnaire (-2.47 vs. -7.27), incidence of grade 3 or higher adverse events higher in tx group vs. placebo (40% vs. 23%).	Pts with <i>BRCA</i> mutations had a longer progression free survival with PARP inhibitor treatment compared to those who received placebo.	Small study. Randomization may have prevented some of cohort from receiving drug even though they may have had significant benefit.	
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Note. Pancreatic ductal adenocarcinoma PDAC, variant of unknown significance VUS, eastern cooperative oncology group ECOG, patient(s) pt(s), poly ADP ribose polymerase PARP, endoscopic ultrasound EUS, national comprehensive cancer network NCCN, past medical history PMH, family history FH, treatment tx, genetic counselor GC, next generation sequencing NGS, impact events scale IES, loss of heterozygosity LOH, Ashkenazi Jewish AJ, Memorial Sloan-Kettering Cancer Center, breast cancer BC, ovarian cancer OC, double-stranded DNA damage repair dsDDR, intraductal papillary mucinous neoplasm of the pancreas IPMN, pancreatic intraepithelial neoplasia PanIN, African American AA, leucovorin fluorouracil, irinotecan and oxaliplatin FOLFIRINOX.

CHAPTER III SYNTHESIS OF THE PANCREATIC CANCER (PC) LITERATURE 2022 - 2023

An update of the PC literature from the time of the article publication (January 2022 – March 2023) including all five themes, with an updated PRISMA diagram, is also provided as Chapter 3, as requested by the dissertation committee.

Introduction

The literature review that served as a foundation for the published practice update was completed in December 2021 as an integrative review. The goal was to explore the diversity of research associated with germline genetic risk assessment and high-risk management of individuals with PC and those at high risk of developing PC in the future. A systematic review would not have captured the various articles that were ultimately reviewed because the chosen literature contained descriptive, qualitative, and mixed methods designs. The integrative review methodology was the best approach to analyze, synthesize, and draw conclusions from this variety of research literature (Whittemore & Knafl, 2005). All articles were summarized into a one-page per article matrix format to manage the data effectively, and this matrix is included following the references as Table 3 in the appendix. The same methodology was followed for this update and is provided in visual form via the PRISMA outline from the initial review in Figure 1. (appendix) and Figure 2. at the end of this chapter.

Initially, there was great interest in incorporating germline genetic testing in PC into the final dissertation study. I became interested in this subject for practical reasons. For the past decade, I have been fortunate to provide care to individuals with PC. This was all too frequently a dire situation. There were very few glimpses of hope for these patients, and yet I have been impressed time and time again by the strength of the human spirit demonstrated by the brave individuals who face this diagnosis and fight it despite overwhelming odds. I have

also been overwhelmed by family and friends' strength and compassion during this terrible period. I have sat face to face with patients too many times to count and shared their diagnosis for the first time and the prognosis associated with it. Too often, I have broken the news that something new was found on a scan, a tumor marker elevated, or we have exhausted all options. I have helped patients and their families decide to meet with hospice and sat through many funerals.

PC is indiscriminate in whom it affects. I have cared for older patients who have lived entire lives before their diagnosis, and I have cared for patients younger than me and gotten to know their children. I still see all their faces. I have chosen this subject because I believe genomic assessment and testing could offer a small glimmer of hope, a silver lining after incorporating genetic risk assessment into my clinical practice. Yes, we may identify treatment options in only a minority of patients, but they are options that were not available before. We may also identify other family members with an increased genetic risk of pancreatic and other cancers. By identifying these family members and providing them with screening, we can locate lesions early and influence treatment outcomes – or maybe even prevent a future malignancy altogether! After almost ten years of clinical practice and only a handful of survivors who have lived for five years past their diagnosis, I saw an opportunity to start turn the tide! I saw an opportunity for the role of nursing. I saw an opportunity for hope.

However, once the data for the study were obtained, unfortunately, insufficient genomic data was available to satisfy any sort of *a priori* power

analysis. The widespread adaptation of germline testing in clinical oncology, especially in PC, is too recent a phenomenon, and not enough of the study cohort had an opportunity to have germline testing. Therefore, the genomic data collected were ultimately not included in the final study and are available for future analysis. However, the collection of these data was beneficial as it, and the initial literature review, directly led to drafting, proposing, and initiating a new high-risk GI clinic (Hi-GI) for those kindreds who genomic testing identified. Therefore, a tangible and evidence-based translational solution has been created, despite this variable not being incorporated into the current study. In addition, the data from a nurse practitioner led point-of-care approach to germline risk assessment for PC patients resulted more than 90% of PC patients at a high-volume PC center being screened and tested in 2022. The results from this quality improvement project were presented as a podium presentation to an international audience of scientists, clinicians, and patient advocates for hereditary gastrointestinal disorders in 2022.

An integrative review update was completed following the same methodology as the earlier literature review. Data were once again gathered using PubMed and CINAHL. Search terms included "pancreatic cancer," "genetics," "germline mutations," and "hereditary risk," applying "and" "or" search options in all combinations with the search terms, as previously done. This search was limited to articles published from when the practice update article was published in January 2022 to the present. A thorough examination of the

articles followed by reading through the titles, followed by reading the abstracts, and then ultimately reading the articles in their entirety when the final articles were identified. The articles were included or excluded based on clinical relevance, and non-peer-reviewed articles were excluded automatically. Duplicate citations were excluded, and a visual representation of this selection process is included as a PRISMA diagram in Figure 2. The five themes identified in the initial review included: Clinical Applications, Gene Identification, High-Risk Screening, Minority Populations, and Therapeutic Applications. These themes were identified based on the subject matter covered in the articles within Table 1. No model was used to identify these themes; instead, the themes were identified after the literature had been thoroughly reviewed. These same five themes are applied to the review update where possible, but the updated review did not reveal literature that could be categorized into all five themes. No new literature, available for review, was identified focusing on increasing minority representation in PC genomics. However, the first phase of a multi-phase, multi-site mixed methods study has recently been completed and will present its' findings at a premier international gastrointestinal conference in May. The updated literature review did not reveal any articles not sufficiently covered by the previously identified thematic sub-categories, and therefore no new themes were required.

Results

The updated literature review followed the same process as the previously described integrative review and revealed twelve articles that met the eligibility criteria. A graphical representation of this process is included in Figure 2 using the PRISMA tool developed by Haddaway et al., 2022. The first theme is the clinical application of germline genomic testing. The theme of clinical application applies to germline risk assessment and testing of individuals with PC and individuals identified as being high-risk. The National Comprehensive Cancer Network recommendations support genetic risk assessment and testing in all individuals diagnosed with PC and thoroughly describe those who would be eligible for testing based on a family history of PC (NCCN, 2023).

Gene identification is the next theme. This theme includes research discovering germline genes identified as precursor genes for PC, studies of the prevalence of these genes, and risks associated with known mutations. This is a ever-changing theme in oncology in general and for PC especially as the genes are known to be associated with PC risk have expanded in the last decade (Ghiorzo et al., 2012, Lucas et al., 2014, Salo-Mullen et al., 2015, Leof et al., 2019). High-risk screening and early detection is the third theme. The third theme of this literature review focused on who is at high risk, what high risk means, and what screening recommendations depend on cancer risk. Because germline mutations vary in their penetrance, and risk for future cancer varies between genes; screening recommendations are truly individualized based on gene

involved, personal health and surgical history, family history of malignancy, and age. Next, the theme of minority representation in germline risk assessment and testing studies in PC patients, their kindreds, and high-risk individuals was identified. Minorities are poorly represented in current research efforts to improve prognosis (McWilliams et al., 2018). Finally, this review will consider the theme of therapeutic interventions and how they are affected by patient participation in genetic risk assessment and testing. This includes therapies designed to capitalize on germline mutation status for oncology treatment.

Each of the five themes is presented individually, and the current state of the science of PC research is discussed. One especially salient detail identified while reviewing articles on this subject was the overall absence of contributions from the discipline of nursing. After reviewing more than 200 articles, only one single contribution was made from the nursing perspective. This represents an opportunity advanced practice nurses to become involved and contribute to improving PC by diagnosing it at earlier stages, designing risk assessment programs, and providing genetic testing. Nurse scientists can become involved by generating new knowledge that will support all of these efforts by defining risk factors, developing best practice approaches based on quantitative analysis, and by providing the patient perspective through qualitative studies that can help drive future clinical efforts for PC patients.

Clinical Application

While most of the clinical application literature reviewed previously (2017 – 2021) focused on alternative treatments or adjuvant treatment to the classic pancreaticoduodenectomy or distal pancreatectomy and splenectomy, a new study from Bagias et al. (2022) examined retrospective data from surgical outcomes and recovery from surgery in individuals with hereditary PC. Interestingly, individuals with hereditary PC had superior surgical results and less eventful recovery from surgery than PC patients with no genetic mutations (Bagias et al., 2022). This finding supports germline testing of all PC patients and may help stratify patients with PC based on surgical risk.

Gene Identification

Genomic applications in clinical oncology are changing rapidly, and it is now routine that genetic assessment of tumors, especially PC, is completed to help personalize treatment (Paredes de la Fuente et al., 2023). In a retrospective study of academic medical center cancer patients, Green et al. (2022) reviewed how many patients with somatic testing underwent germline testing when tumor testing results suggested a possible germline mutation. The study by Green et al. (2022) highlights an important problem with the quick adaptation of emerging technology in clinical practice and the associated risk of not using it appropriately when adapted without fully understanding it. This is a seminal study that defines the dichotomy between what is being done clinically versus what should be done

based on evidence; potential germline mutations identified through tumor testing are frequently observed but not acted upon by follow-up confirmation germline testing. This suggests protocols should ensure these individuals have access to germline testing. After all, germline testing is not just a benefit to the affected cancer patient, but to their family as well. When germline mutations are identified in a cancer patient, they can impact treatment or future surveillance needs. It is equally important, however, to offer testing to unaffected family members to identify who may be at an increased risk of developing malignancy later in life and counsel these individuals on risk reduction and specific surveillance strategies. This article represents the only new contribution to the literature identified and will be a topic of many future studies as genomics become part of every cancer patient's diagnostic and therapeutic pathway.

Another article revealed by this literature update is a review of hereditary cancer risk genes conducted by a National Cancer Institute (NCI) designated cancer center and a commercial genetics lab provides an updated review of individual genes recommended for testing in PC patients, but this does not provide any novel recommendations from the literature reviewed previously (Gardiner et al. 2022). While comprehensive, no additional value or novel concepts are provided by this review.

High-Risk Screening

Seifert and Weitz (2023) published a review and synthesis of familial PC and known hereditary syndromes but more importantly, this study emphasizes importance of enrolling individuals with known hereditary predispositions into registry studies. Participation in these registries is already the standard in Europe, but the US is behind in this effort. These prospective studies will provide novel insights into PC by following these high-risk individuals longitudinally and contributing much needed detail to the basic characteristics of PC patients and how specific variables, such as obesity, may affect PC outcomes (Seifert & Weitz, 2023). An example is the Pancreatic Cancer Early Detection Consortium, PROCEED (Simeone, 2021). Abdel-Razep et al. (2023) review when patients should receive multi-gene panel testing based on their risk for breast cancer, including a family history of PC. This article represents a shift in practice from the articles reviewed previously. As next-generation sequencing (NGS) techniques have replaced more expensive and laborious methods for germline genomic testing, most commercial labs have expanded their testing ability and offer panel testing for clinicians. Panels for germline testing range from as little as two genes to well over 100. The variety of testing now available to clinicians increases the power of germline testing and has resulted in increased numbers of germline pathogenic variants identified. By increasing the number of mutations identified, we are expanding our knowledge of hereditary syndromes, and which pathogenic variants are associated with each cancer diagnoses. This article focuses on the

frequency of negative, positive, and variant of unknown significance results from panel testing in breast cancer patients (Abdel-Razeq et al., 2023). While PC is not the subject of this article, the significance of this work is clinicians need to consider the complexity of family history when assessing patients for their risk. Choice of multi-gene panel can have either a positive or negative impact on its results. If just the patient's diagnosis is considered when choosing a test, a narrow panel may be selected that does not consider family history. This can result in a false negative. Just as a family history of PC in an individual with new breast cancer can be a sign of a potential underlying hereditary predisposition syndrome, a family history of breast cancer is also a risk factor for hereditary PC based on the increased risk of both diagnoses shared across multiple genes (Salo-Mullen et al., 2015).

Lei et al. (2022) published an overview of population-specific screening for BReast CAncer 1 & 2 genes (*BRCA*) mutations in China to help identify individuals at high risk for breast, ovarian, pancreatic, and prostate cancers. This article represents another perspective in providing a regional approach to identifying high-risk individuals. On the other end of the spectrum, Bennett et al. (2022) reviewed high-risk PC syndromes, the genes associated with these syndromes, and the overall risk with each syndrome. This comprehensive review of 79 different studies is a valuable clinical update as it includes cancer-predisposition syndromes and syndromes associated with hereditary pancreatitis but does not offer any new knowledge (Bennett et al., 2022). An article from

Olakowski and Buldak (2022) also focuses on high-risk hereditary syndromes but is less comprehensive than Bennett et al. and does not offer any novel contributions (2022). A final high-risk article focusing on familial PC from Rustgi et al. (2022) provides yet another review of the existing literature on familial PC. While no new concepts are associated with hereditary PC syndromes, this article nicely contextualizes the importance of identifying all individuals at risk for PC; by 2030, PC is projected to be the second leading cause of cancer death (Rustgi et al., 2022). Since PC is relatively rare and the 10th most common cancer diagnosis in the United States, it remains and will increasingly become the most lethal (Siegel et al. 2022). Any efforts to identify disease early have significant potential to improve this prognosis.

Early PC detection remains elusive when a high-risk mutation or a significant family history is absent. Despite the numerous reviews of predisposition syndromes, clinical practice has not improved its ability to diagnose PC at an early stage. However, scientific efforts to identify a precursor to PC continue, and Levin and colleagues (2022) present an example. This study focuses on serum N-glycan monitoring as a PC precursor but reports a specificity of 92%, an accuracy of 90%, and a sensitivity of only 49% (Levink et al., 2022). The potential clinical utility of a serological precursor in PC is that this tool could be used to stratify high-risk patients, and perhaps in the future, it will also improve survival by identifying disease earlier or before it even becomes cancer.

Minority Populations

None of the articles reviewed in the update focused on PC in the minority population in the United States. This is consistent with the findings of The Genetic Education Risk Assessment and Testing (GENERATE) study, but Furniss et al. (2022) and why a new study is being conducted by the same group focusing solely on Black and Latino/a/x high-risk PC individuals in the United States. Clinical trials, whether in genomics or therapeutics, are critical in advancing the science of oncology. Clinical outcomes can only improve when science is advanced, and this requires a diverse population to engage in clinical trials so that translational solutions benefit society, rather than a single homogenous group. The examination of PC in Appalachia focuses on a homogenous population from an ethnic diversity standpoint; however, this population too has historically been under-represented in clinical trials and subsequently has not been on the receiving end of therapeutic and clinical benefit (Zullig et al., 2016).

Therapeutic Applications

The previous literature review was written when the widespread adaptation of genetic testing and targeted therapy was uncommon across the US or other areas worldwide. However, poly adenosine diphosphate-ribose polymerase inhibitors (PARP) were slowly being adopted in breast, ovarian, prostate, and pancreas cancer when the standard of care therapy failed and

previously had been used in clinical trials (Golan et al., 2019). Tsuneizumi et al. (2022) provide a case study of PARP inhibitors used in an individual with PC and a *BRCA* mutation. Their case showed improved clinical outcomes after standard cytotoxic therapy with prolonged survival (Tsuneizumi et al., 2022). While germline mutations are thought to only affect 3-6% of all PC, for individuals with these germline mutations, this therapeutic approach represents a chance for improved outcomes in PC (Seifert & Weitz, 2023).

Kusaga and colleagues (2022) provide an excellent review of PARP inhibitor use in PC by reviewing all genetic syndromes associated with PC and whether PARP is appropriate in individuals with these syndromes. A superb examination of carcinogenesis in these syndromes is provided (Kusaga et al., 2022).

The articles identified since the integrative review offer no new contributions, and do not address the current gaps in therapeutic care; namely use of genomic information to inform clinical treatment choice (Park et al., 2021), or the use of circulating tumor DNA (ctDNA) to change treatment course when PC is not responsive to current regimens (Herreros-Villanueva et al., 2022). ctDNA technology and clinical applications, however, are so new that their utility in clinical decision making is not yet clear. These gaps reveal future scientific opportunity to develop knowledge that will have direct clinical application but remain not fully understood.

Discussion

The integrative literature review update above provides an update of all five themes previously identified associated with high-risk screening, early identification, and treatment of PC. High-risk identification and screening articles and gene identification articles represent the bulk of the update. As previously identified, nurse-led science is absent in the current literature. This remains an opportunity for nurse scientists to determine what factors contribute to late-stage diagnosis of PC, and this knowledge will be used to develop strategies to change this in clinical practice. Nurse-scientist are also well positioned to engage in qualitative studies to understand the barriers to care and barriers to diagnosis that ultimately result in a poor prognosis for PC. Nurse scientists and clinicians are well positioned to improve genomic access for patients through future studies to understand who should be eligible for genomic testing, what patients understand of their genomic results (somatic or germline), and how these results are applied to therapeutic decisions. These are the current gaps that are identified by the original integrative review, and based upon the review update, remain. The studies resulting from this dissertation will help to address a portion of the identified gap.

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Appendix

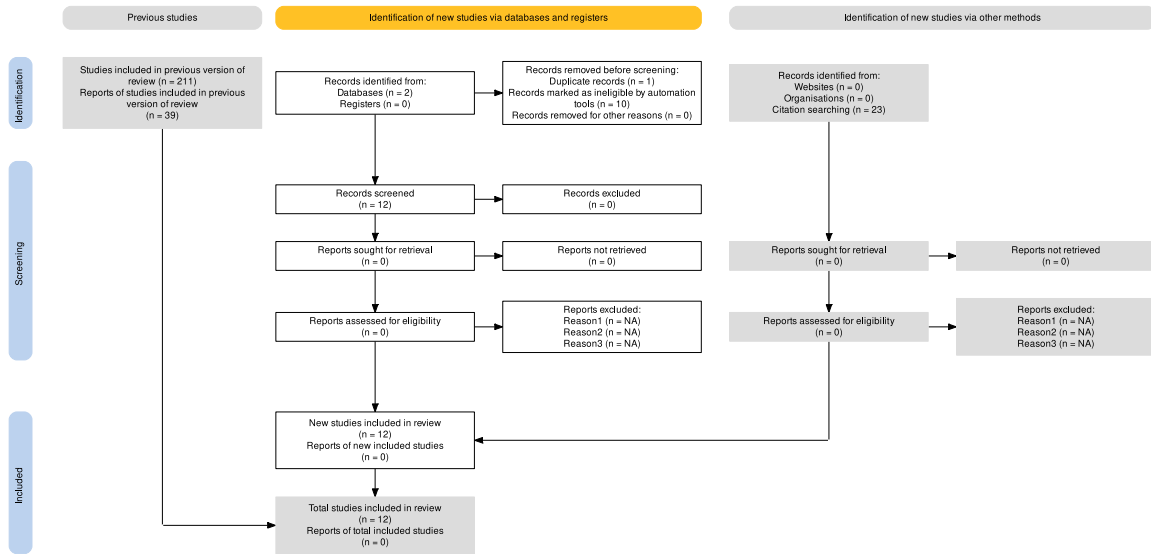


Figure 2 PRISMA from Integrative Review Update: Genomics in Pancreatic Cancer

CHAPTER IV MATERIALS AND METHODS

Chapter 4 is a manuscript format version of the study protocol as recommended by the dissertation committee following PLoS One formatting. Conceptual development, study design, and writing were completed by Andrew J. Ward with recommendation for addition of this information by Dr. Enomoto, Dr. Hutson, and Dr. Lasater and editorial suggestions were made by dissertation committee members Dr. Sangwoo Ahn and Dr. Tami Wyatt.

Introduction

Pancreatic cancer (PC) is relatively rare, being the 10th most common cancer diagnosis in the United States (US) but the third leading cause of cancer death (Siegel et al., 2022). Regionally, South Central Appalachia is affected by PC similarly to the US; however, no studies focusing on PC in this region have been completed to date. This study sought to describe the PC population in South-Central Appalachia by focusing on a single, high-volume PC treatment located within the region of interest as an exploratory analysis. A high-volume PC treatment center is defined as one that averages six to sixteen pancreatic resections per year, with hospitals performing greater than 16 procedures considered as very high-volume (Birkmeyer et al., 2002).

Study Aims

There are three specific aims for the enclosed study.

- Describe the population demographics for PC patients in South-Central Appalachia.
- Assess healthcare and demographic variables for PC patients in South-Central Appalachia for trends over time and space.
- Use ArcGIS to determine if the patient's location is a significant independent variable in predicting PC outcomes.

Materials and Methods

Study Design

A retrospective, secondary data analysis using longitudinal data was conducted. This was a single-site study, with patients presenting to and treated at a high-volume PC treatment center in an academic medical center in South-Central Appalachia. The treatment center averaged 14 pancreatic surgical procedures annually between 2010 and 2020. In three study years, more than 16 procedures were completed per annum. The study used data from the tumor registry and the electronic medical record.

Inclusion/Exclusion Criteria

Participants were selected for this study based on the following inclusion criteria:

1. PC diagnosis includes pancreatic ductal adenocarcinoma, neuroendocrine tumors, and all other PC subtypes reported to local, state, and national tumor registries
2. Diagnosis and treatment or consultation with an oncology specialist (medical, radiation, or surgical oncology) rather than a diagnosis upon autopsy
3. Age 18 and older

Patients presenting to this high-volume treatment center and who did not have treatment or consultation with oncology were excluded. Patients diagnosed with PC upon autopsy were excluded. No individuals identified were under the age of 18 at the time of their diagnosis.

Ethics Approval

This study received EXEMPT approval from the Institutional Review Board (IRB) at The University of Tennessee Medical Center (UTMC) and from The University of Tennessee (UTK) (Study 4974 and 22-07099-XM-RE, respectively). Both IRB offices granted a waiver of informed consent. A data use agreement was also completed between UTMC and UTK.

Data Sources

Data for the study were obtained through data obtained from the study site's tumor registry and the Electronic Medical Record (EMR) of the high-volume PC treatment center. Tumor registry is an office with the hospital responsible for documenting all cancer diagnoses and subsequent treatment received by cancer patients in the facility (Miller et al., 2021). Data collected by the tumor registry is referred to as abstracted data, and this includes all cancer-related information (histological subtype, stage, treatment, dates of diagnosis and treatment, and overall status as alive or dead) and demographic information (name, age, gender, insurance, address) on each cancer patient, but no other health data.

The EMR for the high-volume PC treatment facility was used to provide additional data variables for the PC patients identified by the tumor registry. International Classification of Diseases (ICD) version nine (ICD-9) and ten (ICD-10) codes were used to determine the additional variables of interest and are presented in Table 4. (CMS n.d.a, CMS, n.d.b). Data from the local resources

were used rather than Surveillance, Epidemiology, and End Results (SEER) Program Data because this data does not fully represent the nation, including the study region of interest (SEER, n.d.). After applying inclusion and exclusion criteria to the data provided by the tumor registry, the total sample size is $n = 931$.

Power Calculation

An *a priori* power analysis was performed using z-tests, assessing the difference between two independent proportions (Liu, 2014). G*Power was used in conjunction with expert consultation from a biostatistician to determine the minimum sample size (Faul et al., 2007, G*Power, 2020). For this analysis the dependent variable of health care access, having a primary care provider (PCP), and the independent variable of mortality was used. The null hypothesis is that having a PCP would result in no difference in PC mortality; a two-tailed hypothesis. The anticipated power was set to 0.80, effect size 0.31, allocation ratio of 0.116 to ensure equal sample sizes for a power of 0.80, and $\alpha = 0.05$ (G*Power, 2021). Results from this power analysis suggests a minimum number of patients without a PCP of 94 and a minimum number of patients with a PCP of 815 for a minimum sample size of $n = 909$ was required (G*Power, 2021).

Statistical Plan

The analysis plan for this study was based on the established aims. Missing data were isolated to a single variable; body mass index (BMI). Little's

MCAR test applied to the missing BMI data ($p = 0.998$) determined these missing data points were missing completely at random (Little, 1988). Missing BMI data points were adjusted using mean imputation with a mean BMI of 28.99 (Bannon, 2015). To accomplish Aim 1, descriptive statistics and bivariate analysis were completed using SPSS version 29 for Macintosh. Aim two analysis was performed using bivariate and multivariate methods depending on the normal and non-parametric distribution of the variables. To assess the difference between variables Wilcoxon, Independent t -test, Mann-Whitney U, ANOVA, Kruskal-Wallis, and Chi-squared analysis are used. Pearson and Spearman's analysis is used to evaluate the relationship between variables. Bivariate linear regression and binary logistic regression are used to predict variable changes. And for survival analysis, both Kaplan Meier using log-rank analysis and Cox Regression analysis were completed.

Dependent variables for the analysis include having a primary care provider and then outcome factors for PC, including time to treatment (date of first treatment subtracted from the date of diagnosis) expressed in days, length of survival (date of death subtracted from the date of diagnosis) expressed in months, and mortality (dead versus alive). Independent variables include age, gender, race/ethnicity, driving distance to the treatment facility, total driving time to the treatment facility, insurance status, employment status at the time of diagnosis, and BMI. Additional factors include the presence or absence of the

following diagnoses in the EHR: depression, diabetes, hypertension, hyperlipidemia, pancreatitis, tobacco abuse, and alcohol abuse.

Aim 3 was analyzed using a combination of SPSS and geographical information service (GIS) software ArcGIS Pro 3.0 (ESRI Inc., 2022; IBM Corp., 2022). Using the data from the tumor registry, the variables of driving distance and driving time were calculated for each patient represented in the sample. The software calculated the driving distance from the patient's address using the shortest route to the treatment facility. Parameters were also set defining the day of the week and time of day for travel so that average traffic patterns were considered when calculating driving time to the facility. For this study, drive times were set for Monday at 9:00 am. ArcGIS created additional continuous variables of driving distance to the facility (miles) and driving time to the facility (minutes). These variables were also categorized based on the location being within the metro area surrounding the high-volume treatment facility or drive time radius (Sullivan et al., 2022).

Data Security/Confidentiality

All electronic health data from the tumor registry and EHR was transferred via Secure File Transfer Protocol (SFTP) and saved on an encrypted cloud-based storage drive hosted by University of Tennessee Medical Center (UTMC). Access to the data required two-factor password identification. All data were stored with randomly assigned number designations, and medical record number

and patient name information was removed to anonymize the data further per the established data use agreement. A data audit trail was maintained via a data log throughout the study period.

Discussion

PC is a rare but lethal cancer diagnosis that results in a disproportionate number of cancer deaths—early diagnosis of PC results in improved outcomes of length of survival and overall mortality. The PC population in the South-Central Appalachian region has not been previously described in detail, and it is unclear to what degree healthcare access influences PC outcomes. This exploratory analysis used existing data to examine how healthcare access and comorbidity factors increase the risk for PC impact outcomes in a PC population treated at a high-volume PC treatment facility in South-Central Appalachia. The findings from this study have the potential to identify disparities in PC outcomes between individuals with greater healthcare access by having a primary care provider versus individuals with decreased access. In addition, this study highlights which risk factors are most influential in PC outcomes for the region, allowing for the stratification of PC patients in South-Central Appalachia based on established risk.

Conclusion

In this exploratory analysis, two novel approaches to understand the experience of PC patients in South Central Appalachia were applied. First,

testing for differences in PC mortality based on the healthcare access variable of having a PCP, and second, exploring the role of spatial proximity to treatment center in PC mortality. The role of GIS was critical in determining if the patient's location and proximity to the high-volume treatment center were influential in PC outcomes; an inquiry that has never been presented. Secondary data analyses are often limited in their scope by having few continuous variables available and thus limiting the ability to explore the data. By combining inferential statistical methods with the capabilities of GIS analysis, this study demonstrates it is possible to perform much more robust secondary data analysis when location data is available. The methodological approach allows for the PC population served by a high-volume PC treatment center in South-Central Appalachia to be described in detail for the first time. This knowledge has identified which risk factors are most influential in PC outcomes for the study population.

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Appendix

Table 4 ICD 9 and ICD 10 codes

ICD9 (prior to 2015)	ICD10
Depression: 311, 296.3, 296.21, 296.20	Depression: F32.1
Diabetes: 250.00/250.*	Diabetes: E11.9, E10.9
Heart Disease: 429.9	Heart Disease: I51.9
Hypertension: 401.**	Hypertension: I10
Tobacco Abuse: 305.1, V15.82	Tobacco Abuse: Z72.0
Alcohol Abuse: 303	Alcohol Abuse: F10.10
Hyperlipidemia: 272.***	Hyperlipidemia: E78.5
Obesity: 278.02	Obesity: E66.9
Pancreatitis: 577.****	Pancreatitis: K85.90, Z87.19
- *Any suffix digit will still be diabetes - **Any suffix digit will be hypertension - ***Any suffix digit will be hyperlipidemia - **** Any suffix digit for pancreatitis	

**CHAPTER V IMPACT OF HEALTHCARE ACCESS ON
PANCREATIC CANCER OUTCOMES IN SOUTH-CENTRAL
APPALACHIA**

Chapter 5 will be submitted for publication by Andrew Ward. This chapter is a combination of two individual manuscripts developed from the dissertation study. The first manuscript is the Health Access Behavior Analysis of South Central Appalachian Pancreatic Cancer Patients. The second manuscript, included as Chapter 6, and is a Survival and Spatial Analysis of South Central Appalachian Pancreatic Cancer Patients. Conceptual development, data analysis, and writing were completed by Andrew J. Ward with editorial suggestions were made by dissertation committee members Dr. Sangwoo Ahn, Dr. Laura Enomoto, Dr. Sadie Hutson and Dr. Tami Wyatt.

Abstract

Pancreatic cancer (PC) is a rare cancer diagnosis, yet it is the third leading cause of cancer death in the United States. Patients with the best prognosis are those with early-stage disease who are surgically resectable. No current strategies exist to identify PC early, outside of specific high-risk individuals.

This study aims to describe population demographics for PC in South-Central Appalachia, to identify variables that may aid in future early PC identification, and to assess if the patient location is a significant independent predictor of PC outcomes.

A retrospective, secondary data analysis assessed cross-sectional tumor registry data on PC patients at an academic medical center in South-Central Appalachia. Data were obtained from tumor registry and the electronic health record on PC patients treated from 2010 through 2020. Health access by having a primary care provider (PCP) was assessed, along with demographic and comorbidity health factors associated with PC were assessed for influence on PC

outcomes of stage of disease upon presentation, time to treatment, overall survival duration, and mortality.

931 patients with PC were included. The mean age of diagnosis was 67.0; 52% (484) were male, and 89.8% (836) identified as white. 69.8% (650) of the patients presented with Stage IIb, III, or IV disease. The mean distance to the treatment facility was 56.6 miles, mean driving time was 49.8 minutes. Having a PCP, being younger, having health insurance, and living closer to the treatment facility had a positive influence on overall survival and were associated with more rapid time to treatment.

This study shows age, insurance, patient location and proximity to treatment facility, and access to primary care independently affected overall survival.

Introduction

Pancreatic cancer (PC) has a terrible prognosis and is the third leading cause of cancer death in the US (Niederhuber et al., 2013; Siegel et al., 2022). Most PC is ductal adenocarcinoma (85%), with rare histology types including neuroendocrine tumors, signet-ring cell type, and even squamous cell rounding out the remaining 15% (Park et al., 2021). Prognosis is enhanced when patients are eligible for surgical resection. Unfortunately, only 15 – 20% of patients are candidates for pancreaticoduodenectomy or distal pancreatectomy, depending on the location of the malignant lesion (Niederhuber et al., 2013). For those patients who complete resection and have perioperative systemic and radiation therapy, five-year survival is approximately 30% if there is no nodal involvement and only 10% when disease extends locally into the lymph nodes (Niederhuber et al., 2013). Historically, PC is often identified too late for surgical intervention for patients who would tolerate these procedures. As a result, only a small proportion of patients affected by PC will ever have a 10-30% survival prognosis in five years following diagnosis.

Background and Significance

Approximately 62,000 patients in the US will be diagnosed with PC in 2023 (Siegel, 2022). PC commonly affects people after age 45, but earlier diagnosis can occur. Men are more affected than women (1.3:1), and black

Americans have a disproportionately worse outcome than white Americans (McWilliams et al., 2018).

Risk factors for PC include modifiable lifestyle factors such as tobacco use, obesity, physical inactivity, a diet high in saturated fats and processed meats, excessive alcohol consumption, and diabetes mellitus with insulin resistance (Bosetti et al., 2012; Carreras-Torres et al., 2017). Hereditary factors also play a significant role, including a family history of PC and specific genetic predisposition syndromes (Grant et al., 2015; Shindo et al., 2017). Familiarity with these clinical and hereditary factors by clinicians is a critical component to early identification of PC.

Early PC does not present with specific clinical signs or symptoms. Instead, when patients present with symptoms, PC is usually at an advanced stage (Blackford et al., 2020). At this point, signs and symptoms associated with PC include painless jaundice, hepatomegaly, cachexia, weight loss, epigastric and back pain, nausea and vomiting, diarrhea, and steatorrhea (Porta et al., 2005). An additional clinical sign is a recent diagnosis of profound diabetes mellitus (Batabyal et al., 2014). Initial evaluation of these symptoms often includes abdominal ultrasonography, computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), and either percutaneous or endoscopic ultrasound-guided (EUS) biopsy for tissue diagnosis. Often this work-up can be protracted and delayed due to access issues to specific services or specialty

providers resulting from geographical, financial, and healthcare navigation barriers (Lukács et al., 2019). Clinicians can play a critical role in identifying early signs and symptoms of PC and facilitating timely and appropriate referrals to manage new PC cases appropriately. A thorough understanding of local referral resources, including gastroenterologists, who can perform EUS and ERCP, and interventional radiologists who can perform biliary drainage, is essential for efficient diagnosis.

The best chance of identifying PC at an early stage is to offer high-risk screening to individuals who meet the criteria for being at increased risk of developing PC based on either medical history, family history, or genetic predisposition. Clinicians caring for individuals affected by chronic pancreatitis, especially with a family history of pancreatitis and no personal history of alcohol abuse, should recognize this as a risk factor for future PC (Rebours et al., 2012). Hereditary risk factors for PC include hereditary pancreatitis and a family history of two or more primary relatives diagnosed with PC (Klein et al., 2004; Tersmette et al., 2001). A family history of PC is detected by reviewing the patient's medical history or checking it when establishing a new patient to a clinic and documenting their family history. Several genetic syndromes increase the risk of developing PC, and a concise review of these disorders is provided by Ward (2022).

Prior studies have demonstrated that the optimal outcomes in PC occur when patients have access to a high-volume PC treatment center (Birkmeyer et al., 2002). According to this landmark study, a high-volume PC center is one that

completes six or more pancreatic surgeries annually, including pancreatic resection for non-malignant reasons. For PC patients, this often means an academic setting is the best choice for treatment. High-volume PC centers can also be advantageous for high-risk patients with a history of pancreatitis who require PC surveillance. These patients will have unique nutritional and metabolic needs and are best served in specialty centers with improved resource access (Arutla et al., 2021).

Factors such as tobacco use, obesity, physical inactivity, diets high in saturated fats and processed meats, excessive alcohol consumption, and diabetes mellitus also increase the risk of developing PC (Bosetti et al., 2012, Carreras-Torres et al., 2017). In South-Central Appalachia, these factors are all reported at rates equal to or higher than the rest of the US (Beatty et al., 2019; Wilson et al., 2016). Too often, the literature describing healthcare in Appalachia focuses on disadvantages and poor outcomes compared to non-Appalachian regions in the US. Despite having high rates of disorders associated with increased risk of and poor prognosis for PC, this study explored the possibility that with access to appropriate resources, individuals with PC in South-Central Appalachia can have similar or even improved outcomes compared to the rest of the country.

This study aims to evaluate if the stage of PC presentation and overall survival after PC diagnosis is influenced by healthcare access, specifically having a PCP. Stage of presentation is a critical predictor of survival in PC. As

previously established, prognosis in PC is best when patients are diagnosed before advanced-stage disease. Time to treatment is also a key component in improving prognosis once a diagnosis of PC is made. Access to PC treatment is hypothesized to not significantly affect presentation stage, time to treatment, overall survival duration, or mortality in PC patients in South-Central Appalachia because the biological nature of PC is so deadly.

Research Design and Methods

Conceptual Framework

The conceptual framework for this analysis is the Behavioral Model for Vulnerable Populations (BMVP) which takes inspiration from Andersen's Behavioral Model of Health (BMH) (Andersen, 1995; Gelberg et al., 2000). In 2000, Andersen and colleagues presented the BMVP in response to contemporary reductions in benefits to individuals receiving coverage from state and federal healthcare programs considered vulnerable. These included minorities, immigrants, children, elderly, mentally ill, and economically disadvantaged individuals (Gelberg et al., 2000). The BMVP builds upon the prior BMH by including attributes or "domains" specific to vulnerable populations. These broad domains include immigration status, receipt of public benefits, and diagnoses associated with vulnerability (acquired immunodeficiency syndrome or AIDS, for example). This approach provided a framework for understanding health behaviors by looking at individuals and circumstantial health determinates.

In their meta-analysis of the Andersen model, Babitsch and colleagues (2012) provided many examples of the individual attributes of the BMH. The predisposing factors in this model are demographic factors that are non-modifiable. Enabling factors are attributes that, when present, facilitate the ability of an individual to access health care. Need factors are those attributes that would create a reason for an individual to access healthcare. The model developed for this study is illustrated in Figure 3. which demonstrates how these factors influence healthcare access for PC patients in South-Central Appalachia.

Predisposing factors include age, gender, ethnicity, and distance to the high-volume PC treatment center. Enabling factors include financial and access characteristics. Economic factors from the Andersen model include region of residence, employment status, and health insurance status. Enabling factors for PC patients in this study include having access to a regular source of health care (primary care provider, (PCP)) and spatial access to available care, i.e., distance to/total drive time to the high-volume PC treatment center. Need factors within the Andersen model are divided into individual and environmental need factors. Individual need factors include chronic disease (e.g., hypertension, diabetes) diagnoses concurrent to PC.

Under the Andersen BMVP model, other predisposing, enabling, and need factors affecting healthcare utilization have been identified and included in the analysis to determine their role in influencing PC outcomes in South Central Appalachia.

Methodological Approach

A retrospective data analysis was used for this exploratory analysis. Given the grim prognosis of PC as a disease, a retrospective analysis is a reasonable approach to portray the population of interest and establish a baseline description. Independent variables within the dataset collected were not manipulated in any way, and therefore the study design is nonexperimental or observational and representative of the entire study population (Polit and Beck, 2012). A correlational design using inferential statistical analysis and geospatial analysis was employed to determine if common dependent variables shared throughout the study population affected stage of presentation and overall survival.

Data Collection

An academic medical center in South-Central Appalachia (Figure 4.) with a high-volume pancreas service, mean PC surgery of 14 per year, was used as a source of the retrospective PC data (Birkmeyer et al., 2002). Inclusion criteria included a diagnosis and receiving treatment for PC, being over 18 years old, and having accessible data within the electronic medical record. Exclusion criteria included having a cancer diagnosis but not receiving treatment at the study facility, post-mortem diagnosis of PC, and being under 18. A descriptive summary of the population, including the predisposing and enabling factor variables selected from the BHVP model, is presented in Table 2 and the

population spatial distribution is in Figure 5. Institutional Review Board approval for the research was granted by The University of Tennessee Medical Center and The University of Tennessee Institutional Review Boards (Study 4974 and 22-07099-XM-RE, respectively). Both organizations approved the study as exempt based on the proposed retrospective secondary data analysis. Written, informed consent was not required. A Data Use Agreement was established between the researcher and the academic medical institution, outlining the approved use of the requested data. All data were anonymized for analysis by the author once the dataset was complete. Identifying medical record numbers were deleted, and random identifying numbers were assigned. All names and dates of birth were deleted. While personal health information such as residential address and date of diagnosis was approved for inclusion by the IRB, medical record numbers, names, and dates of birth were not authorized to ensure the patients' anonymity.

Data were collected using the tumor registry at the academic medical center. The academic medical center serves a 21-county catchment area in East Tennessee, and surrounding counties from Eastern Kentucky, Southwest Virginia, and Western North Carolina. Individuals diagnosed with PC and treated at the academic medical center had their charts abstracted by the local tumor registry staff. This abstracted data included demographics, patient address, PC-specific histology/pathology information, treatment information about systemic therapy provided, surgical interventions, and radiation therapy, date of diagnosis,

stage of disease on diagnosis (AJCC 8th edition), date of initial treatment, date of last contact, date of death or status (still alive) (Amin, 2017). After an initial data review, duplicates from seven individuals (same individual entered under different medical record numbers) were omitted. Additional data were collected from the electronic health record (EHR) including comorbidities such as depression, diabetes, hypertension, heart disease, hyperlipidemia, history of pancreatitis, tobacco use, alcohol abuse, and obesity.

Data Analysis

Abstracted data from Tumor Registry did not include several variables of interest. IT at the academic medical center ran parallel reports to determine if the patients in the population had diagnoses of chronic diseases associated with an increased risk for PC (Ward, 2022). International Classification of Diseases (ICD) version nine (ICD-9) and ten (ICD-10) codes were used to determine the additional variables of interest (CMS n.d.a, CMS, n.d.b). An IT automated query did not identify all individuals in the data set, so 178 manual chart reviews were required to complete the data set. Univariate and bivariate analysis including ANOVA, binary logistic regression, bivariate logistic regression, Chi-squared analysis, Independent *t-test*, and Mann-Whitney U were used. Data were analyzed using SPSS Version 29 for Macintosh and ArcGIS Pro 3.0 (ESRI Inc., 2022; IBM Corp., 2022).

Results

The Tumor Registry data request identified 931 (N = 931) participants. The mean age of patients with PC was 67.05 (SD 11.44). 74.3% of the patients had advanced disease (ie, stage IIb – IV), and staging information was not available for 55 (5.9%) patients in the cohort. The median survival was 17.13 months (range: < 30 days – 146.17 months; SD + 23.87). The overall five-year mortality was 75.5% and the remaining descriptive and enabling factors are summarized in Table 6. The survival characteristics of South-Central Appalachia's PC population are summarized with a comparison to the State of Tennessee and National PC characteristics in Table 5. A summary of the healthcare access, and need factors selected for the BMVP model analysis are presented in Table 7.

Chi-squared analysis reveals a significant difference ($\chi^2 = 3.825$ (1), $p = .050$) between individuals with a PCP (210, 93.3%) and individuals without a PCP (15, 6.7%) who were diagnosed with localized PC (n = 225). No significant difference ($\chi^2 = 3.267$ (1), $p = .071$) was identified in mortality based on having a PCP. Bivariate logistic regression was used to assess whether having a PCP or not could predict a change in overall survival duration. The overall model was not significant (-2LL = 621.47, $p = .373$) and explained only 0.2% of the variance in length of survival by Nagelkerke R^2 . Individuals with a PCP survived only 0.4% longer than individuals without a PCP (OR = 1.004; CI = .995 – 1.014). This model correctly classified PC patients by having a PCP 89.6% of the time.

Bivariate logistic regression was also used to assess if having a PCP resulted in an earlier time to treatment. The overall model was significant ($-2LL = 609.65$, $p = .007$). Individuals with a PCP were 3.5% more quickly to advance on to treatment from diagnosis than PC patients without a PCP ($OR = 1.035$; $CI = 1.010 - 1.061$). The overall model resulted in correct classification of PC patients having a PCP 89.6% of the time.

Examining the predisposing factor of age using binary logistic regression reveals a significant influence on mortality ($-2LL = 1008.21$; $p < .001$). For every year older a patient is upon diagnosis, their risk of survival decreases by 4.5% ($OR = .965$; $CI: .952 - .978$). Age and length of survival were also significantly related ($R = .248$), as revealed by bivariate linear regression. Assumptions of normality and linearity were met, and as the age of PC diagnosis increased by one year, the length of survival decreased by 0.518 months ($p < .001$). Factors of gender and ethnicity had no significant influence on PC outcomes.

The enabling factor of insurance status significantly influenced the time to treatment ($f = 15.983$ (6), $p = .014$) for the insured versus the uninsured. The chi-squared analysis also demonstrated a significant relationship between insurance status ($\chi^2 = 24.45$ (6), $p < .001$) and mortality. Length of survival (months) differed significantly based on insurance status as demonstrated by ANOVA ($F = 4.660$ (6), $p < .001$). The no-insurance group had a mean survival of 15.29 ($SD \pm 23.02$), commercial insurance 24.61 ($SD \pm 27.38$), Medicaid 17.48 ($SD \pm 24.83$), Medicare 14.76 ($SD \pm 22.27$), and the VA/IHS group 18.23 ($SD \pm 25.50$). A

significant difference in length of survival was noted between the commercial insurance group and the Medicare group ($p < .001$) only. Employment status at diagnosis influenced overall mortality ($\chi^2 = 15.55(4)$, $p = .004$). A patient's place of residence significantly influenced the stage of their disease, as demonstrated by Chi-squared analysis ($\chi^2 = 20.79(6)$, $p = .014$). The distance traveled to the high-volume facility resulted in a difference in the length of overall survival, as demonstrated by ANOVA ($F = 3.40(3)$, $p = .017$). Drive time was categorized into driving radii of 30 minutes or less (mean = 15.63 months survival; $SD \pm 22.43$), 60 minutes or less (mean = 18.02; months $SD \pm 24.59$), 90 or less (mean = 20.74 months; $SD \pm 27.32$), and greater than 90 minutes (mean 11.37 months; $SD \pm 15.18$). Time to treatment and mortality were not significantly influenced by place of residence.

Need factors had less influence on PC outcomes than either predisposing or enabling factors. Individuals with a history of pancreatitis (mean = 15.05; $SD: \pm 20.29$) who were diagnosed with PC had a significant difference in overall survival duration compared to those without a history of pancreatitis (mean = 25.55; $SD: \pm 33.50$) ($p < .001$) as determined by an independent *t*-test. Obesity was a negative predictor of mortality ($-2LL = 1029.72$; $p = .009$). A diagnosis of obesity increased the risk for mortality by 50.8% (OR 1.508; CI 1.109 -2.050). There was a statistically significant difference in overall survival between patients who were obese upon diagnosis of PC and those not by Mann-Whitney U analysis ($p < .001$). By binary logistic regression, tobacco abuse was a negative

predictor for mortality ($-2LL = 1028.47$; $p = .006$). Those who used tobacco were 40.3% less likely to survive PC (OR = 0.597; CI 0.414 – 0.862). Those with a history of alcohol abuse (mean = 7.88 months; SD $\pm$ 8.7) ($p < .001$) had significantly shorter survival than those who did not (mean = 17.39 months; SD $\pm$ 24.12). No other need factors had a significant effect on the PC outcomes.

Implications

For the first time, this study describes the PC population in South-Central Appalachia in a detailed and systematic manner. This sample representing South-Central Appalachia had some surprising results when using Andersen's model for health behaviors in vulnerable populations. Despite Appalachia, in general, being disproportionately affected by many of the reported risk factors associated with PC, this population was overwhelmingly unaffected by chronic diseases of diabetes, hypertension, and obesity. In addition, the study population was also mostly non-smoking and did not have a history of alcohol abuse.

This analysis indicates that individuals with the greatest survival are diagnosed younger and who live neither too close nor too far from a high-volume treatment facility. These patients have disease identified at an earlier stage, have a shorter time to treatment interval following diagnosis and have the greatest duration of survival. For the South-Central Appalachia population with PC, this underscores the vulnerable status of the population. Patients who lived furthest from the high-volume treatment center and those who live adjacent to the

treatment center in a more urban environment had decreased mean survival duration compared to individuals who live in more suburban areas. This finding underscores the vulnerability of a patient's location. Location vulnerability is not just a product of their proximity to the treatment facility.

Enabling factors of insurance and having a PCP also suggest a positive influence on PC outcomes for the region, demonstrating that healthcare access (having a PCP) conveys an advantage to PC patients. Healthcare inaccessibility is a phenomenon created by many factors, including lack of accepted health insurance coverage and inconvenient location of healthcare services in the county of residence (Morrone et al., 2021). This finding is especially relevant in a setting where many Appalachian regions experience a moderate to high shortage of healthcare providers according to the Health Resources and Services Administration; this includes Morgan County, Grainger County, and Union County within the 21-county catchment area of the high-volume treatment center (HRSA, 2023).

Finally, an examination of chronic disease states (diabetes, obesity, pancreatitis, alcoholism) that are often associated with an increased risk of developing PC shows that in South Central Appalachia, individuals with risk factors of obesity/increasing BMI, tobacco abuse, and a history of pancreatitis experienced an overall decreased length of survival with a greater risk of death compared to the PC individuals in the same cohort who did not have these conditions and health habits.

These findings carry broad implications for the population of interest and future health disparities studies in South-Central Appalachia. First, these findings help researchers and clinicians focus on specific areas of disparity to help work towards more equitable outcomes. For example, tobacco cessation programs and assistance in maintaining a healthy weight could improve the baseline population health. In this study, for example, individuals who were obese, abused tobacco, and had a history of alcoholism had worse PC outcomes when compared to those who did not have these modifiable risk factors. Second, policy efforts to improve healthcare access by expanding state and federally-managed insurance options for those who are currently underinsured, as well as efforts to expand access to primary care, will benefit from the findings of this and similar studies that show the improved outcomes when individuals have access to these healthcare services even in circumstances of PC. Finally, this study that used secondary data analyses to identify specific areas for healthcare improvement may offer insights that influence community leaders, clinicians, public health officials, and policymakers to improve outcomes at the population level. This type of study is a valuable investment for a historically disadvantaged region like Appalachia and will pay off by supporting a healthier, more productive population.

Limitations in this study include those of any retrospectively collected database, including limitations associated with obtaining data from chart reviews. The data can only be as accurate as the source it is obtained from. Results may not be generalized to PC patients in the region of South-Central Appalachia who

do not have access to a high-volume PC center (Figure 6. demonstrates national high-volume centers), chose to seek treatment elsewhere, chose alternative therapies, or who chose not treatment at all for their PC. The study has several strengths to off-set these weaknesses. This study is the first to present a large cohort of PC patients in South Central Appalachia and can serve for a baseline comparison for future studies. Also, the use of Andersen's BMVP demonstrated the important role PCPs can play in influencing cancer outcomes. Finally, this study demonstrated that there are modifiable risk factors that impact PC outcome, and identification of these factors presents an opportunity to improve outcomes for PC patients. Development of translational clinical solutions to address smoking, obesity and alcohol abuse have potential to improve PC outcomes independent of PC directed therapies.

Overall outcomes for the study population were better than those for PC patients in Tennessee. This likely reflects the phenomenon of PC patients having improved outcomes at high-volume PC centers such as the site where data were retrieved for this study (Thomas et al., 2022). Future studies examining larger geographic areas of Appalachia, including areas less densely populated and without access to high-volume PC centers, are warranted and would likely reveal regional nuances in PC individuals.

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Appendix

Conceptual Model Health Care Access in South Central Appalachia Pancreatic Cancer Patients

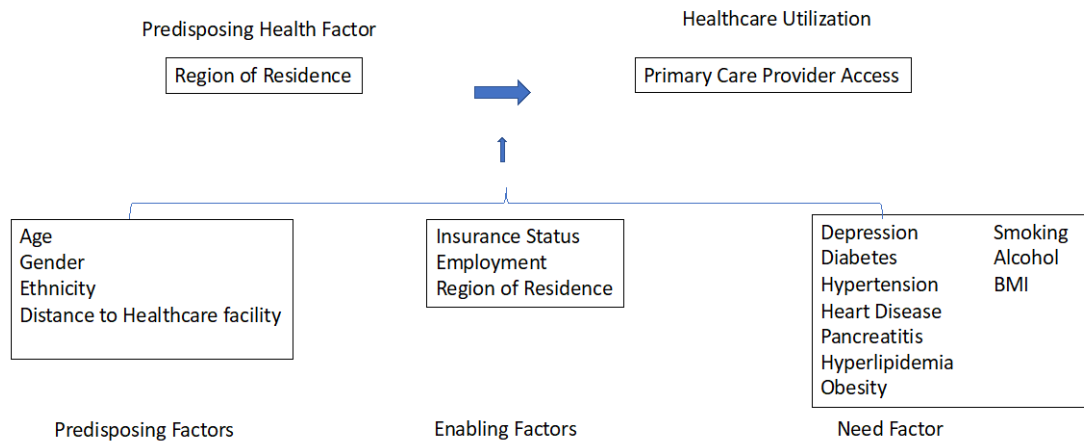


Figure 3 Conceptual Framework

Table 5 Incidence and Five-year Mortality Characteristics Pancreatic Cancer Compared to Tennessee Tumor Registry Data and National Trends (SEER)*****

	S.C. Appalachia*	Tennessee**	US***
	N = 931	N = 5,185	N – 62,210 [⊥]
Gender (female)	442 (47.4%)	2503 (48.3%)	47%
Average Age of diagnosis	67.05	x	x
Mortality	703 (75.5%)	4,576 (89%)	49,830 (80.1%)

Note: * Current study population 2010 – 2020, **2014 – 2018 Richards & Whiteside, 2022, *** Siegel et al., 2022, x = data not reported, ⊥ estimated cases for 2022.

Table 6 2010 – 2020 South Central Appalachia Pancreatic Cancer population descriptive summary, including Andersen’s BMVP Enabling Factors

Variable	Descriptive Statistic (N = 931)
Age	67.05 (11.44)*
Gender (female)	442 (47.4%)**
Ethnicity	
Asian	0
Black	50 (5.4%)**
Latin/Hispanic	8 (0.9%)**
White	836 (89.8%)**
Native American	0**
Refused/missing	37 (4%)**
Distance to Healthcare Facility	26.62 (13.55 – 45.94)***
Driving Time	38.75 (24.11 – 62.82)***
Insurance Status	
No insurance	38 (4.1%)
Private/Commercial Insurance	207 (22.2%)**
Medicaid	39 (4.2%)**
Medicare	610 (65.5%)**
Military/Veteran	14 (1.5%)**
Indian Health Service	1 (0.1%)**
Unknown	22 (2.4%)**
Employment	
Unemployed	476 (51.1%)**
Employed	359 (38.6%)**
Refused to respond	0
Student	1 (.1%)**
Retired	75 (8.1%)**
Unknown	20 (2.1%)**
Mortality	703 (75.5%)**
Overall Survival (months)	17.13 (23.87)*
Time to Treatment	7.01 (21.80)*
Stage of Presentation	
0	11 (1.2%)**
I	24 (2.6%)**
Ia	33 (3.5%)**
Ib	78 (8.4%)**
II	19 (2.0%)**
IIa	60 (6.4%)**
IIb	167 (17.9%)**
III	115 (12.4%)**
IV	369 (39.6%)**
Unknown	55 (5.9%)**

Note: * Mean (Standard Deviation), ** Frequency (percentage), *** Median (interquartile range), Mortality = alive/dead, TTT = Time to treatment (date of initial treatment subtracted from date of diagnosis), OS = overall survival in months

Table 7 Andersen's Behavioral Healthcare Access Model for Vulnerable Populations: Pancreatic Cancer Patients in South-Central Appalachia
Andersen's Healthcare Access and Need Factors

Variable	N = 931	N = 931
Healthcare Access Factor	Incidence	frequency
PCP *	834	89.6%
Need Factors		
Depression *	72	7.7%
Diabetes *	376	40.4%
HTN *	661	71%
Heart disease *	32	3.4%
Hyperlipidemia *	492	52.8%
Pancreatitis *	185	19.9%
Obesity *	321	34.5%
Tobacco use *	245	26.3%
Alcohol abuse *	26	2.8%
BMI **	29.0	24 – 37.7

Note: * Incidence (percentage), ** Median (interquartile range)

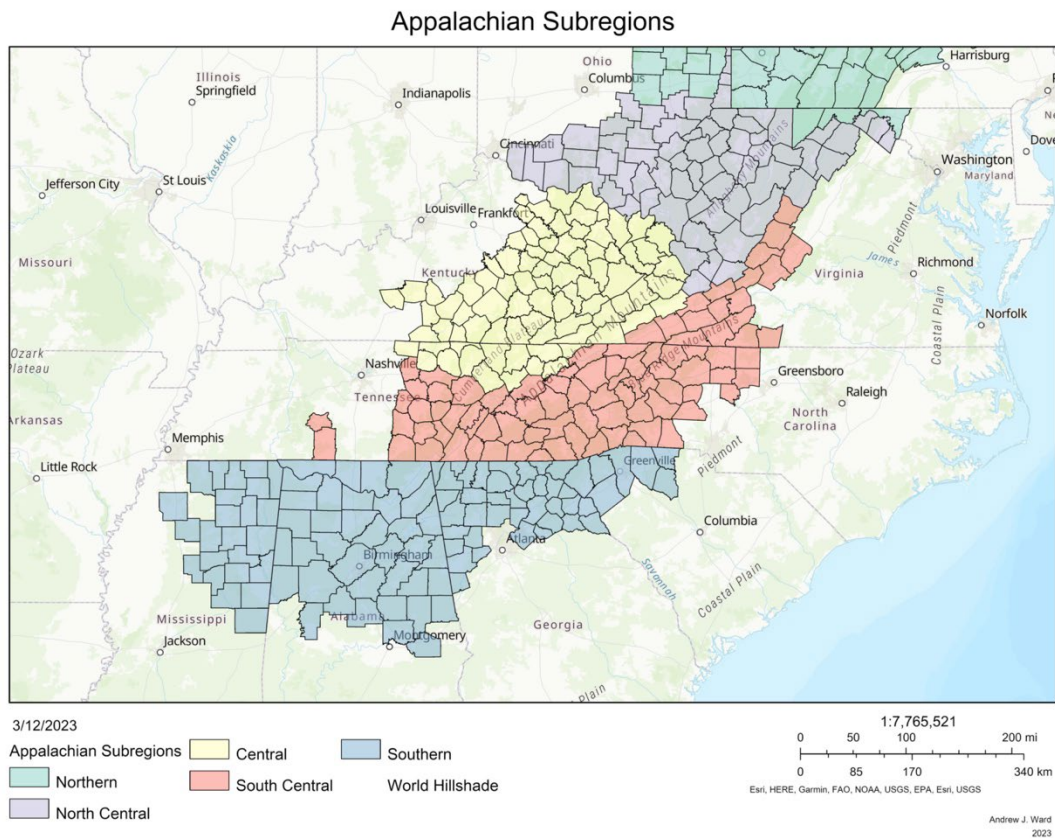


Figure 4 Regions of Appalachia

Note: Graphical representation of Appalachian sub-regions, Andrew J. Ward ArcGIS Pro (2023)

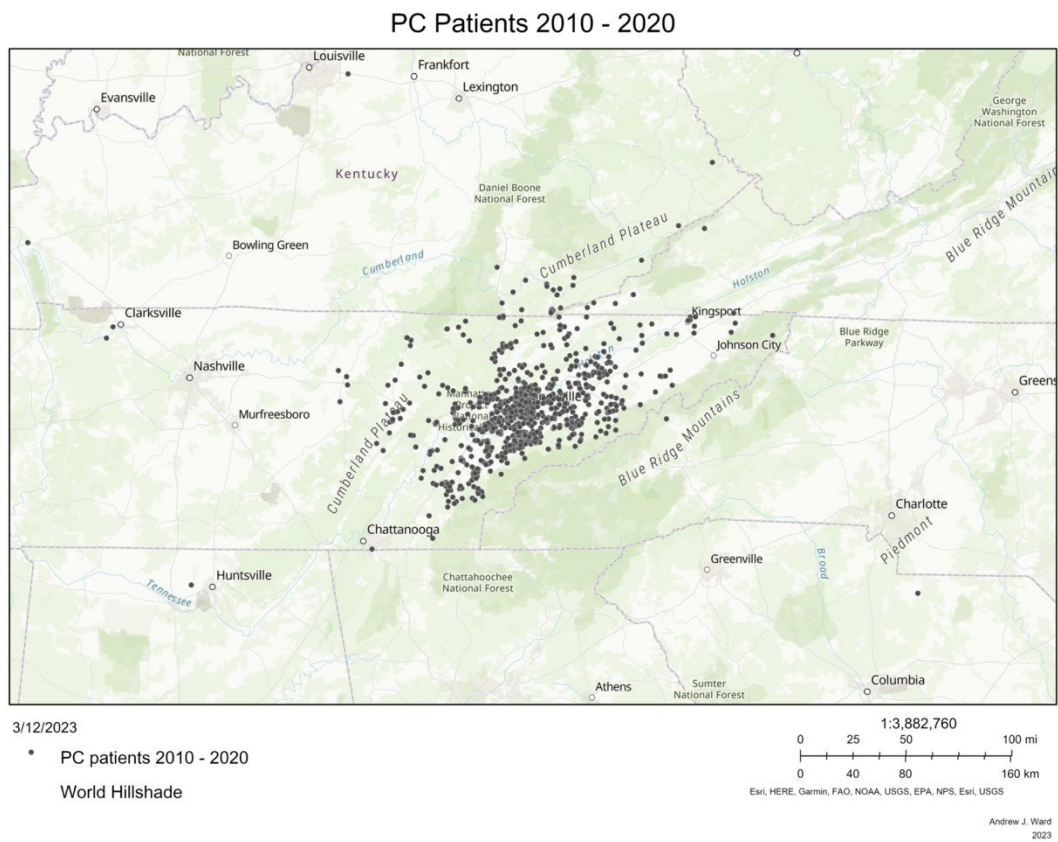


Figure 5 Distribution of study participants

Note: GIS map showing geographic distribution of study patients, Andrew J. Ward ArcGIS Pro (2023)

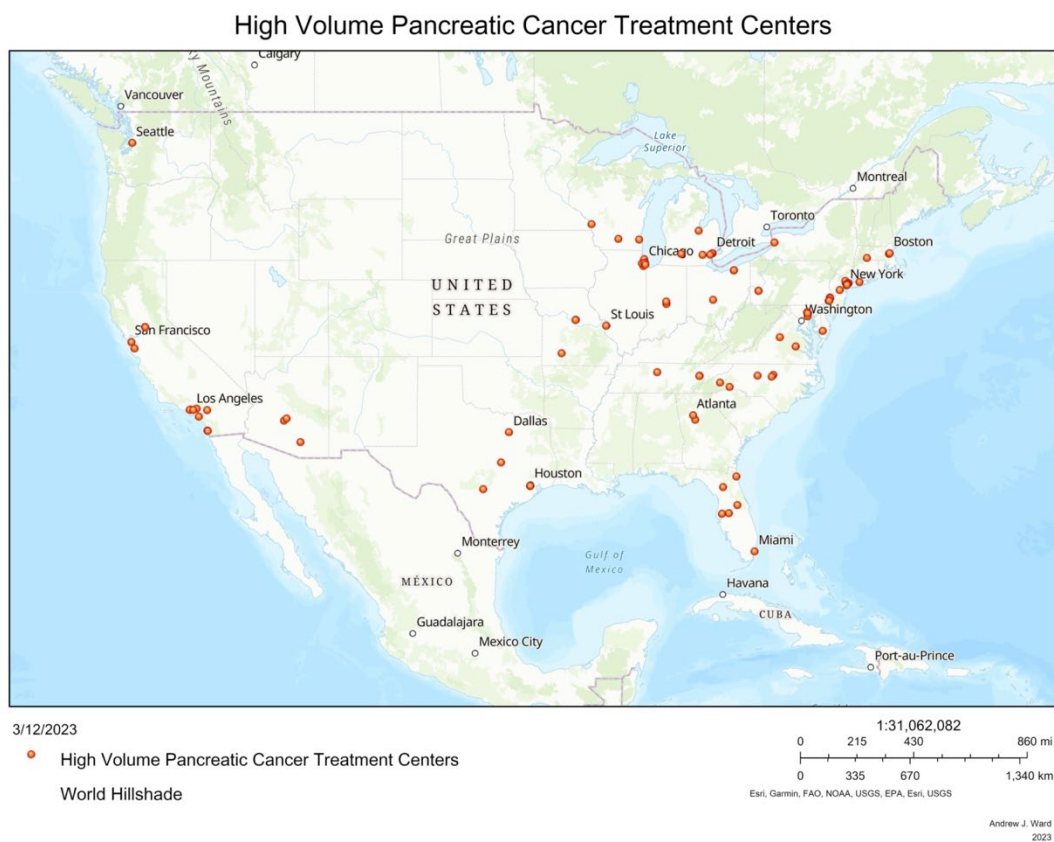


Figure 6 Location of high-volume pancreatic cancer treatment centers (US)

Note: GIS map showing geographic distribution of study patients, Andrew J. Ward ArcGIS Pro (2023)

CHAPTER VI PANCREATIC CANCER IN SOUTH-CENTRAL APPALACHIA: THE GOOD, THE BAD, AND SILVER LINING

Abstract

Pancreatic cancer (PC) is rare compared to breast, lung, or colorectal cancer but is the third leading cause of cancer death in the United States. Patients with early-stage disease have the best prognosis but represent less than 35% of all cases. Factors such as tobacco abuse, alcohol abuse, obesity, and diabetes are thought to increase the risk of PC. It is unclear how these factors affect PC outcomes. It is also unclear how patient geographic residence affects PC outcomes.

This study evaluates how health factors associated with PC risk and their effect on cancer outcomes in South-Central Appalachia. This study also explores the effect of patient geographic residence on PC outcomes.

Methods: This retrospective cohort study analyzed a prospectively collected tumor registry of subjects diagnosed with pancreatic cancer at a high-volume center in South Central Appalachia from 2010 – 2020. Patient demographics, comorbidities, and distance to hospital were analyzed to determine their effect on mortality. Spatial analysis was conducted using ArcGIS Pro.

A cohort of 931 PC patients was collected. Individuals with a diagnosis of tobacco abuse, alcohol abuse, and obesity had decreased 5-year overall survival compared to individuals without these comorbidities. Individuals who lived within 30-minute drive time to the treatment facility presented were more likely to have Stage IIa or earlier PC and had longer 5-year overall survival. Mortality did not differ between those who lived close to the treatment facility and those who lived

further away. Individuals treated at the high-volume center had an overall decreased mortality rate than for overall PC mortality in Tennessee.

Identifying comorbidities in PC can help stratify those patients at greatest risk for mortality. This information can guide clinicians toward individualized care based on regional variation. Patients living greater than 90-minute drivetime to the high-volume center tend to present with later-stage disease and are at higher risk for progression.

Introduction

The incidence of pancreatic cancer (PC) is estimated to be over 62,000 individuals in the US in 2022, and it is the third most common cause of cancer death (Siegel et al., 2022). In Tennessee, PC is the 11th most common cancer diagnosis but represents the fourth most common cause of cancer death for Tennesseans. From 2014 – 2018, 89% of Tennesseans with PC died (Richards & Whiteside, 2022). Prognosis for PC is improved when patients are diagnosed at an early stage, and are eligible for surgical resection of their tumor.

Unfortunately, many patients diagnosed with PC present with advanced-stage disease and therefore do not qualify for surgery (Niederhuber et al., 2013). The presentation of PC at a later stage is the result of many known and unknown factors; one reason is signs and symptoms associated with PC are often non-specific and not evident until the disease is no longer localized and, therefore, overall survival (OS) is significantly decreased compared to PC patients diagnosed with localized disease (Blackford et al., 2020; Batabyal et al., 2014; Porta et al., 2005). These unknowns suggest opportunities for improving the prognosis of PC by better understanding the population it affects and how the traits of that population influence the outcomes of the disease.

The etiology of delayed PC presentation is multifactorial, with the ambiguity and late association of typical signs and symptoms only one factor. Additional reasons for delayed PC presentation include difficulty in detection and diagnosis, requiring specialized diagnostic imaging and clinical skills, and access

to these diagnostic tools is often limited to large, well-funded healthcare organizations (Lukács et al., 2019). Still, other factors leading to the delayed diagnosis of PC remain unknown. A review of the current PC literature reveals a wealth of studies on novel treatment approaches and genomics, but few studies focus on how PC affects individual populations. There are no studies that examine the PC population in South-Central Appalachia. Several studies have examined health behavior factors and other social determinants of health to understand why disparities in PC outcomes exist between racial groups in the US, but to date, no studies have examined how location impacts the stage of presentation and overall survival in PC (Papageorge et al., 2021; Poulson et al., 2022; Thomas et al., 2022). While studies demonstrating differences in outcomes between ethnic and socioeconomic groups are valuable and have helped reveal existing health disparities, they are specific to the sample populations they represent. Finally, additional studies have demonstrated that patients diagnosed with PC who receive treatment at a high-volume PC center have improved outcomes compared to those who have not received treatment at a high-volume center (Birkmeyer et al., 2002). High-volume PC centers, however, are rare and often associated with academic medical centers in densely populated areas. This study is novel because it examines healthcare factors from a cohort of PC patients in South-Central Appalachia not previously reported in the literature.

Health factors such as tobacco use, obesity, physical inactivity, diets high in saturated fats and processed meats, excess alcohol consumption, and

diabetes mellitus are thought to increase the risk of developing PC (Bosetti et al., 2012, Carreras-Torres et al., 2017). In South-Central Appalachia, these factors are all reported at rates equal to or higher than the rest of the US (Beatty et al., 2019; Wilson et al., 2016). To what degree these factors affect overall survival for PC patients in South-Central Appalachia is unknown. To address the role of geospatial access as a healthcare access variable, independent of tumor biology in PC, a geographic information system (GIS) based model was constructed to evaluate the relationship between modeled travel time, stage of presentation of PC, and overall survival of PC patients in South-Central Appalachia. These findings will also support the premise that individuals with PC have improved outcomes when treated at a high-volume center.

Methods

Retrospective data were collected, and a secondary data analysis using convenience sampling was completed. Independent variables including diabetes, history of pancreatitis, tobacco use, alcohol abuse, and obesity were selected from the data to represent known risk factors for PC. An academic medical center in South-Central Appalachia with a high-volume pancreatic service (averaging fourteen pancreas surgeries annually during the study period) serving middle and eastern Tennessee, eastern Kentucky, western North Carolina, and Southwest Virginia was the source of the secondary dataset (Birkmeyer et al., 2002). Study inclusion criteria were: 1) diagnosis and treatment for pancreatic

cancer in the medical center's tumor registry, 2) 18 years of age and over, and 3) have accessible electronic medical record data. Exclusion criteria included: 1) PC diagnosis but no treatment at the study facility, 2) PC diagnosis at the study facility upon autopsy, and 3) age under 18. Institutional Review Board approval (Study 4974 and 22-07099-XM-RE) for the research was granted as exempt based on the proposed retrospective secondary data analysis. Written informed consent was not required. All data were anonymized before examination by the author once the dataset was completed.

The dataset obtained from the tumor registry included basic PC patient demographic information, patient address, PC-specific histology/pathology information, treatment information related to surgical procedures provided for systemic therapy, and radiotherapy. These data variables provided by the tumor registry (specifically street-level address data including city, county, and state) supported GIS analysis of the study population and provided additional variables of distance to the treating facility and travel time to the treating facility for each patient represented. Using the capabilities of GIS created new variables for each patient in the sample, including drive time (minutes) and driving distance (miles) from a patient's residence to the treatment facility. Date of diagnosis, disease stage at diagnosis, date of initial treatment, and date of death or current vital status (still alive) were also included in the data set provided by the tumor registry. The staging of PC is based on the 8th edition of the American Joint Committee on Cancer Staging Manual (Amin. 2017). Overall survival was

calculated from the date of presentation to the date of death from any cause or last contact.

The high-volume PC treatment facility and the residential locations of the patients were geographically located using ArcGIS Pro (version 3.0; ESRI, Redlands, California). The place of residence for individual patients within the cohort was obtained from the tumor registry. GIS calculated the distance to the treating facility using the most direct route following primary (highway), secondary (interstate), and tertiary (minor and unpaved roads) with the aid of ArcGIS Pro. Travel time was calculated based on traffic patterns from the residential location to the treatment facility for the study environment on a Monday at 9:00 a.m., assuming the most direct and efficient route from the residence to the treatment facility.

Logistic regression was used to determine the effect of travel time on stage of the presentation. Cox Regression analysis characterized with 95% confidence intervals examined the relationship between mortality and geospatial access. Kaplan-Meier 5-year survival analysis and log rank test compared patients living within 30, 60, 90, and over 90 minutes of drive time to the high-volume pancreatic cancer center versus overall survival time and mortality (Sullivan et al., 2022). These methods allow for both understanding of the event's risk and time to the event over a defined period (overall survival measured in months) between groups. In this case, the groups represented various distances from the treatment facility. A graphical representation of the study population and

distribution throughout these drive-time areas is presented in Figure 7. The Kruskal-Wallis test was used where appropriate, as data were non-parametric in distribution. A significant result was defined as $p < .05$. All statistical analyses were performed using SPSS software (v29 for Macintosh; IBM).

Results

Between January 2010 and December 2020, 931 patients presented to the high-volume pancreatic cancer center for diagnosis and treatment. Place of residence location data was available for 927 patients (99.6%). The mean age of PC patients was 67.05 (SD 11.44). 74.3% of the patients presented with advanced disease (i.e., stage IIb – IV), and staging information was unavailable for 55 (5.9%) of the patients in the cohort. The mean length of survival for PC patients was 17.13 months (range: less than 30 days – 146.17 months; SD $\pm$ 23.87), and overall five-year mortality was 75.5%. 32.4% of the cohort had surgical intervention for the PC. Systemic cytotoxic therapy was provided to 550 (59.1%) patients, and 203 (21.8%) had radiation. Complete baseline characteristics for the cohort are included in Table 8. The median travel time for the cohort was 38.75 minutes (IQR 24.11 – 62.82 minutes). Patients with a history of alcohol abuse were 65.4% (OR = 1.654; CI: 1.081 – 2.531) more likely to die of their PC (-2LL = 8616.93 (1); $p = .020$). Patients who smoked were 18.6% (OR = 1.186; CI: 1.007 – 1.397) more likely to die than non-smokers (-2LL = 8616.86 (1); $p = .041$). Diabetes was not significantly (OR = 0.879; CI: .755 –

1.022) associated with a decreased 5-year overall survival (-2LL 8618.10 (1); $p = .094$). Obesity was associated with a 25.1% (OR = 0.749; CI: .639 - .878) reduction in 5-year overall survival duration in PC patients (-2LL = 8607.75 (1); $p < .001$).

PC patients who lived furthest from the academic medical center were more likely to be diagnosed at an advanced stage of disease ($p < .001$), and individuals with localized disease (Stage 0 – IIa) were more likely to live closer ($p = .017$) to the facility. Mortality was not significantly affected by a patient's home location and proximity to the high-volume treatment center; 5-year mortality for the study cohort was 75.5%. No significant difference in overall survival (measured in months) was identified (see Figure 8.) whether a patient lived within 30, 60, or 90-minute drive time to the treatment facility ($p = .155$). Individuals who lived within a 30-minute drive-time to the facility had a 12.4% increased overall survival time compared to those who lived beyond a 30-minute drive-time ($p = .089$).

Implications

In this retrospective cohort study, healthcare factors of tobacco abuse, obesity, and alcohol abuse were all associated with a decreased length of 5-year overall survival in this sample of PC patients from South-Central Appalachia. Diabetes, however, did not significantly influence PC outcomes in this cohort. These findings were congruent with previous literature, apart from diabetes not

impacting overall survival (Bosetti et al., 2012, Carreras-Torres et al., 2017). Diabetes affected 40.4% (376) of participants in this sample. Identifying these factors is a critical first step toward improving the prognosis for all PC patients and can pave the way for a regionally specific approach to patient care. The knowledge gained from this study can be used to develop interventions tailored to PC patients with high-risk factors (and those without) concurrent with their cancer diagnosis. While these factors are common to the region in general, future patients in South-Central Appalachia with a new diagnosis of PC and any of these factors associated with a worse prognosis may benefit from earlier referral to adjuvant services such as Palliative Care or even Clinical Trials. This finding also underscores the significance of preoperative rehabilitation as treatment of PC has shifted towards a neoadjuvant approach, even in patients surgically resectable upon diagnosis (Aziz et al., 2019).

Patients with longer drive times had advanced stages of PC. This finding is independent of biological and clinical factors (e.g., tumor location and treatment method) associated with PC outcomes. Reduced geospatial access to the high-volume PC center did not significantly influence overall survival; however, no other high-volume pancreatic center was within the region to provide other treatment options. Future research that includes a qualitative component to determine patient motivation in facility choice is needed to better understand this phenomenon. Clinically, individuals who lived within the 30-minute drive-time radius of the treatment facility significantly increased their length of overall

survival. Overall survival was not expected to be substantially influenced by patient location based on the lethality of PC. However, individuals living closer to the facility sought care earlier in the disease and experienced a prolonged survival. These findings likely represent healthcare access variables not defined in this study. This means an opportunity for future research using a larger sample and with expanded geographic representation.

This study also contributes to the literature demonstrating that individuals with PC treated at a high-volume center have improved outcomes compared to those not treated at high-volume PC treatment centers. This finding is most evident when comparing the mortality rate for the study cohort (75.5%) to that of the mortality rate for PC patients reported by the tumor registry for Tennessee (89%). Further research is warranted to understand this difference better, as it is not known precisely where Tennesseans sought their care, if they received treatment for their diagnosis, or if PC was identified on autopsy but is still included in the state-reported data. A novel revelation from this study is that distance to the high-volume center is associated with an earlier stage of diagnosis and increased length in overall survival. Additional studies with larger cohorts and different geographical areas are warranted to understand better the role of proximity to a treatment facility in cancer outcomes.

Finally, this study represents a bright spot, a silver lining for healthcare in Appalachia. Despite the grim prognosis associated with PC, this sample of patients from South-Central Appalachia had improved mortality among a subset

of individuals by having access to the high-volume center and when compared to national trends for PC mortality (Siegel et al., 2022).

The findings from this study demonstrate that academic medical centers are a true asset for the communities they serve; in part, they provide access to resources that are often unavailable at community hospitals that may be closer or more convenient for patient access. In addition, patients can often receive treatment at academic medical centers, specifically through the emergency department, whether they have insurance or not, further underscoring the value of these organizations to their community (Lozano et al., 2015). Investment and support in academic medical centers represent an investment in the community's healthcare. Academic medical centers are also training the next generation of clinicians and researchers who will further support the health of the communities they serve.

This study demonstrates congruence with existing evidence-based science; treating patients requires looking at the whole patient and not simply their diagnosis to provide the most effective care. PC patients have opportunities to personalize care based on regional variation. The study demonstrates that patients with specific comorbidities can be stratified into a category of higher risk for PC progression, suggesting opportunities to employ prehabilitation techniques in addition to standard-of-care treatment. From the policy perspective, the findings from this study underscore the need to promote wellness initiatives to improve population health. Support of smoking cessation, maintaining a healthy

body weight, and treatment of alcohol abuse disorder will not only improve outcomes for future PC patients in Appalachia but will support a more healthy and productive community in Appalachia. This study also supports removing barriers that reduce access to care.

Further research is needed to understand precisely where these barriers impact care. The spatial analysis completed in this study reveals the pragmatic truth that the further away patients are from healthcare, the greater their morbidity. This phenomenon has been demonstrated in other regions (Wasif et al., 2016; Lidsky et al., 2017; Siegel et al., 2021) This revelation was unexpected in a disease like PC and suggests future application of this methodology to other conditions affecting the people of Appalachia may also reveal similar findings. This knowledge helps support efforts to increase access to healthcare by expanding insurance coverage, increasing the number of providers in both rural Appalachia and suburban Appalachia through both recruitment of new clinicians and expansion of the scope of practice to advanced practice providers such as Nurse Practitioners and Physician Assistants who are already within these needy communities.

Limitations in this study include the representation of a single PC population with access to a high-volume PC treatment center. These patients may have skewed outcomes (with superior outcomes) compared to PC patients in the same region who do not have access to the high-volume treatment center. Another limitation of this study is the use of ArcGIS to create the critical variables

of travel time and travel distance for each patient. This method requires access to street-level data to achieve its potential, and this may not always be possible with all datasets. This study also does not account for PC patients who chose not to have treatment for their disease, were identified with PC upon autopsy, or decided on non-traditional methods and whose outcomes are not represented.

Finally, this study represents a bright spot for healthcare in Appalachia. Despite the grim prognosis associated with PC, this study's patients from South-Central Appalachia have demonstrated equal or improved outcomes compared to the national trend by having access to the high-volume center and when compared to national trends for PC mortality (Siegel et al., 2022). This represents this study's single most significant implication: secondary data analyses allow for a more holistic understanding of complex medical issues such as PC. By identifying factors that enable patients to be stratified based on their risk for disease progression, clinicians and researchers can develop translational approaches to move toward improving overall prognosis by offering personalized care based on factors beyond biology. If this can be done for something as deadly as PC, this method could be applied to more common healthcare issues. This could have widespread impact on public health and public policy and improve the population health for Appalachia as a whole.

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Appendix

PCMapwSubRegions&Drivetimes

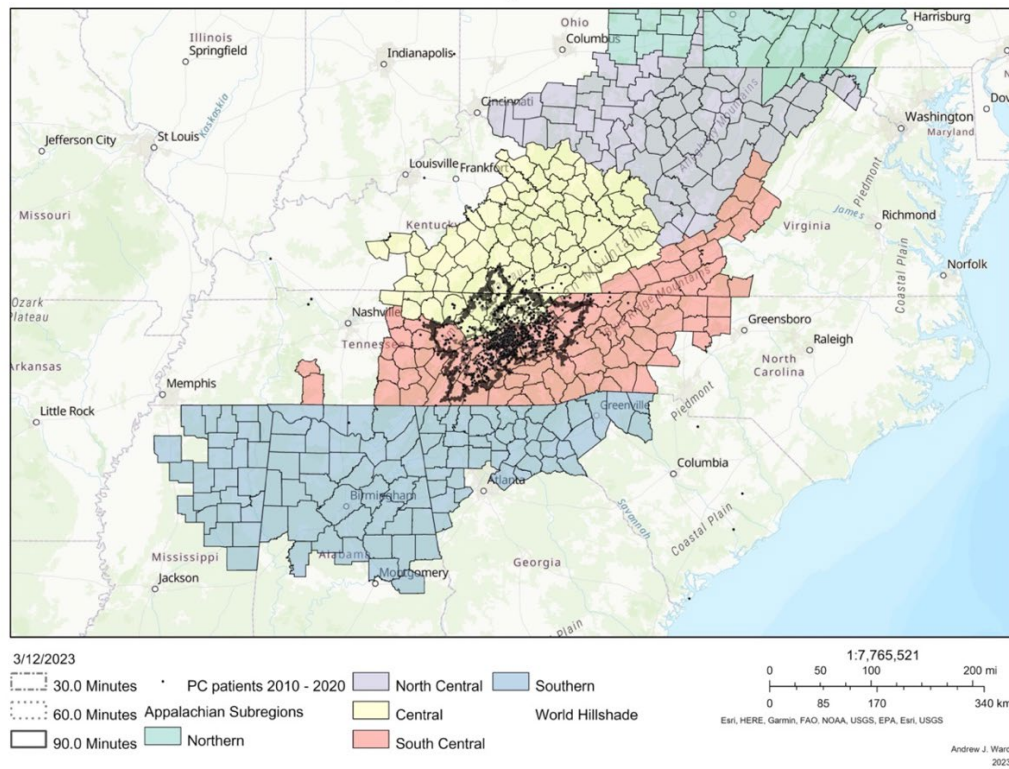


Figure 7 ArcGIS Map Demonstrating Pancreatic Cancer Patient distribution and 30, 60, and 90-minute Drivetime.

Note: Produced in ArcGIS Pro (Ward, 2023)

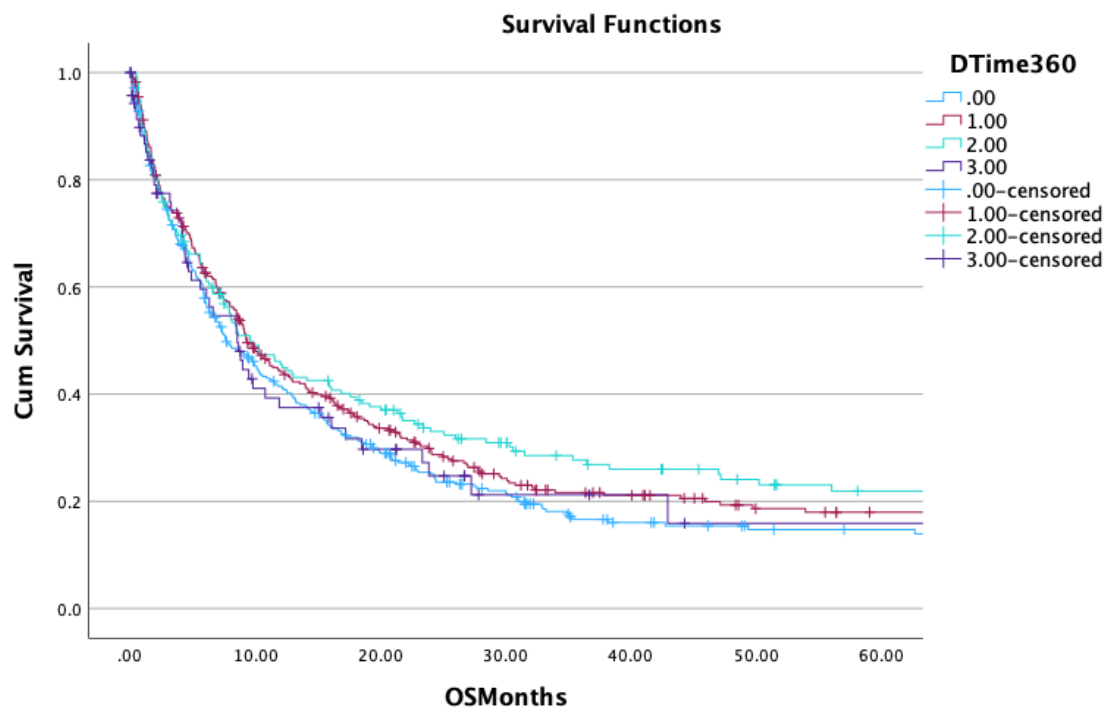


Figure 8 Kaplan Meier Five-Year Survival Curve (Overall survival by travel time to high-volume PC treatment center)

Note: Overall survival with censored event being “alive.” PC individuals stratified by travel time to academic high-volume PC treatment center.

Table 8 Pancreatic Cancer Cohort Attributes (2010 – 2020 South-Central Appalachia High-Volume Treatment Center)

Variable (N = 931)	
Age*	67.05 (11.44)
Gender** (female)	442 (47.4%)
Ethnicity	
Asian	0
Black**	50 (5.4%)
Latin/Hispanic**	8 (0.9%)
White**	836 (89.8%)
Native American**	0
Refused/missing**	37 (4%)
Distance to Healthcare Facility***	26.62 (13.55 – 45.94)
Driving Time***	38.75 (24.11 – 62.82)
Insurance Status	
No insurance	38 (4.1%)
Private/Commercial Insurance**	207 (22.2%)
Medicaid**	39 (4.2%)
Medicare**	610 (65.5%)
Military/Veteran**	14 (1.5%)
Indian Health Service**	1 (0.1%)
Unknown**	22 (2.4%)
Employment	
Unemployed**	476 (51.1%)
Employed**	359 (38.6%)
Refused to respond**	0
Student**	1 (.1%)
Retired**	75 (8.1%)
Unknown**	20 (2.1%)
Mortality (alive/dead) Median follow-up 17/13 months**	703 (75.5%)

Table 8 Continued

Overall Survival (months)* Range < 30 days – 146.17 months	17.13 (23.87)
Stage of Presentation	
0**	11 (1.2%)
I**	24 (2.6%)
Ia**	33 (3.5%)
Ib**	78 (8.4%)
II**	19 (2.0%)
IIa**	60 (6.4%)
IIb**	167 (17.9%)
III**	115 (12.4%)
IV**	369 (39.6%)
unknown**	55 (5.9%)

Note: * Mean (Standard Deviation), ** Frequency (percentage), *** Median (interquartile range)

CHAPTER VII CONCLUSION & DISCUSSION

Conclusion

This dissertation is comprised of three manuscripts, each with a different perspective on pancreatic cancer (PC). The introduction reviews the rationale for approaching the phenomenon by providing an overview of PC etiology, incidence, morbidity, and mortality of PC, and known risk factors for PC. Following chapters 1 and 2 is the study of PC in South-Central Appalachia with goals of increasing PC awareness in the community and ultimately identifying variables that may lead to future ability to improve disease prognosis for PC patients. The articles in chapters 5 and 6 represent first-of-their-kind efforts to describe PC in the Appalachian population—publication and dissemination of the findings enclosed in these articles bring PC awareness to several venues. Pancreatic cancer has never been the subject of a published article by the Journal of Appalachian Health, a potential target journal for a manuscript in the future. In addition, a public presentation and a national conference are scheduled for the local community.

The introduction concludes by reviewing the aims of the current study, the significance, the theoretical framework applied to the second article (chapter 5), assumptions, research questions, limitations, and delimitations of the study. Chapter 2 is a practice update published in The Journal for Nurse Practitioners on PC, its risk factors, and practical implications for nurse practitioner clinical practice. This article was initially submitted as an integrative review but rejected as too long for publication and irrelevant to nurse practitioner practice. Editorial

staff from the Journal for Nurse Practitioners, however, felt the content appropriately highlighted the need for nurse practitioners and other clinicians to have an opportunity for increased awareness of PC. Thus, the article presented in chapter 2 was reworked and published as a practice update. This contribution provides clinicians with an overall description of PC, signs and symptoms, and appropriate clinical workup. It also includes a summary table of all PC-associated high-risk and genetic risk factors for provider reference. Finally, chapter 2 includes, as an appendix, a graphical representation of the literature review, a matrix containing a description and categorization of each article reviewed. Chapter 3 is a literature review update covering articles published from the time of the practice update until present.

Chapter 4 is a detailed description of the materials and methods used in this study. The specific aims of the study are recapitulated. The study design and ethics approval are described. The data sources are defined, and the details of the data variables obtained from each source are outlined. A description of the extrapolation of the co-morbidity variables is provided. A power analysis for the Andersen's BHVM analysis is reviewed and the statistical plan is revealed.

Chapter 5 is the first of two manuscripts created from the data generated by this study. The first manuscript collects data on PC patients in South-Central Appalachia treated from 2010 to 2020 at a high-volume PC treatment center/academic medical center in the study setting. Using the theoretical framework of Andersen's Behavioral Model in Vulnerable Populations (Gelberg et

al., 2000), evaluating various factors associated with PC patients for their influence on the outcomes outlined in chapter one.

Analysis of data from the organization's tumor registry and electronic medical records to determine relationships between independent and dependent variables chosen from the PC patients using statistical software (SPSS v29) aided by geographical mapping and exploration software (ArcGIS Pro). This combination of methodology resulted in novel variables being accessible to evaluate relationships between biological, social, and spatial variables. For example, patient location of residence data was available through the tumor registry. Without the aid of ArcGIS Pro, this data point would not be of significant interest or use in the overall analysis. However, with the tools available through ArcGIS Pro, individual patient location of residence data could be transformed into new continuous variables of driving distance (miles) to the treatment facility and driving time (minutes) to the treatment facility. These variables were converted further within SPSS v 29 to categorical variables, including whether patients lived in metropolitan Knoxville or within a specific drive time to the facility.

Variables allowed for the spatial aspect of the study to be completed and allowed for questions of the data to be asked about PC outcomes and patient location of residence. The potential social, clinical, and policy implications associated with including the spatial analysis of the PC population include increasing PC awareness in the metropolitan area surrounding Knoxville, where

the greatest impact of PC is measured. For example, the Cancer Support Community of East Tennessee, located in Knoxville, may find that it would be worthwhile to increase its pancreas programs. The data analysis and the visualizations provided by the ArcGIS analysis showing PC distribution in East Tennessee (and beyond) make a compelling story with practical graphical representation. The clinical implication resulting from the use of ArcGIS is that having a primary care provider (PCP) has a significant influence on outcomes such as stage of disease upon presentation, time to treatment, and overall survival. The first two outcomes are predictors of 5-year overall survival, which suggests having a PCP assists patients in accessing care earlier.

Certainly, policy implications mirror the social and clinical implications, and the results of this study could support policy issues that would reduce barriers to access healthcare, such as increasing the number of providers in rural areas and expanding the scope of practice to advanced practice providers such as nurse practitioners and physician assistants. Another manuscript prepared for publication is a survival analysis using spatial parameters of the PC dataset curated for chapter 5.

The second manuscript, in chapter 6, provided a different view of the variables analyzed in the previous chapter and the only multivariate analysis of the available data. Survival analyses using Kaplan Meier and Cox Regression analysis were employed to portray the difference in survival outcomes based on the patient's location of residence. In addition to providing a spatial-survival

perspective of the PC patients represented in this study, this manuscript also ties back to the premise of PC patients having improved outcomes at high-volume centers first mentioned in the introduction, but also in chapter 2, the published practice update. This was not the intended outcome from the onset of preparing this article. Additional research is necessary to determine how PC patients in this study compare to those in the same geographic region who did not have access to a PC high-volume treatment center.

Both manuscripts presented in chapters 5 and 6 are formatted generically and will be reworked to meet the publication requirements for the target journals identified for each manuscript. The knowledge generated by these manuscripts represent essential findings that can potentially improve health outcomes for PC patients in the Appalachian region. For example, identification of specific risk-factors that affect PC outcomes in this study will allow for evidence-based practice solutions to be created that are tailored to the specific risk factors of tobacco use, alcohol abuse, and obesity. Programs for smoking cessation, alcohol abuse treatment, and weight loss designed as interventions that nurse navigators and advanced practice nurses implement in PC treatment centers can reduce the disparate outcomes demonstrated by this study. For example, alcohol abuse was seen in only 2.8% of the cohort and resulted in a significantly reduced duration of survival. Addressing obesity would impact both survival duration and mortality in PC patients, and successful smoking cessation strategies would directly improve mortality for PC patients. These factors are not specific risk

factors to PC, but to wellness in general. The general public who interprets the results of this study can identify that these risk factors are personally modifiable risk factors that they can actively take part in controlling. For those who are at an increased risk to develop PC based on personal history, family history, or an identified genetic predisposition, this knowledge is power, the personal power to actively control one's risk.

The results described here underscore that while traditionally considered disadvantaged, resources available to the population represented in this particular portion of South-Central Appalachia provide best practices and improved outcomes for the community. While this is an unintended silver lining for health care in Appalachia, a more critical opportunity remains. This study used data from the tumor registry and the electronic medical record to retrospectively look at selected variables in PC patients to determine how these variables influenced PC outcomes. This allowed for relationships between previously untested variables to be explored and resulted in the discovery of some unanticipated relationships between patient location of residence and stage of PC upon diagnosis, patient location of residence and overall survival, having access to a PCP and stage of presentation as well as the length of overall survival. Other relationships between the variables and outcomes were expected, such as being a smoker and having a decreased overall survival duration, having a history of alcohol abuse or pancreatitis, and having a decreased overall

survival. Through this work, we can understand the impact distance to care and access to care has on PC outcomes at a high-volume PC treatment center.

This study fits into a larger context of research conducted in Appalachia using similar quantitative and spatial techniques. Public health has long used this combination of techniques to examine various phenomena. In 2012, Burgoine and colleagues used GIS data in a cross-sectional analysis of body weight in relation to environmental exposures in a North Carolina pediatric population. This study demonstrated that the walkability of children's route from neighborhood to school affected healthy body weight. Similar to this study, GIS provided a much-needed continuous variable and valuable insight into the role of spatial location and its impact on the critical health indicator of body weight. Pedigo et al. used GIS data to supplement health outcomes data in stroke and myocardial infarction patients to identify areas with increased mortality risk (2011). Like the dissertation study, Pedigo et al. (2011) proposed that this methodology was a valuable tool for identifying high-risk communities and can guide programs designed to address disparities that result in poor health outcomes. More recently, Mann et al. (2021) examined the role of everyday gatherings in Appalachian communities, such as churches, schools, and nursing homes, played in early Corona Virus (COVID-19) outbreaks in the early days of the pandemic. Spatial visualization using GIS was critical in understanding the connection between areas of congregation in rural communities and these early outbreaks.

The use of quantitative and spatial analysis is also not new to nursing research. In 2017, Edward and Biddle used GIS to augment their analysis of healthcare barriers Hispanic and Latino immigrants face in the South. GIS data demonstrated how location and distance confounded transportation and socioeconomic factors as primary barriers to equitable healthcare access (Edward & Biddle, 2017). Kane and Topmiller (2022) used GIS data to support their premise that nurse-midwives are essential in expanding access to opioid-use disorder treatment. The subject of cancer is also addressed by nursing research using the combined methodological approach of quantitative and spatial analysis. Khang et al. (2016) used GIS data and the same survival analysis methods of Kaplan Meier and Cox Regression analysis to demonstrate the role distance to screening facilities plays in follow-up for abnormal mammograms.

Multi-disciplinary teams have applied similar methodological techniques to address chronic disease. A multi-disciplinary group used GIS to assess the distribution of end of life resources available to individuals with HIV/AIDS in Appalachia (Hutson et al., 2020). Once again, the spatial location and visual representation ability of GIS were critical to the success of the aims set forth by this multi-disciplinary team. Finally, Basara and Yuan (2008) used GIS data to demonstrate the correlation between environmental conditions and health outcomes. GIS data was a vital component of more extensive quantitative analysis. This study, in particular, served as a useful early example of the

usefulness of GIS data and its spatial representation of data in multivariate health studies.

This brief review shows how the dissertation study fits into the larger state of the science using quantitative analysis and spatial analysis techniques in Appalachia, and even more examples could be provided from regions worldwide. GIS applications, including quantifying spatial distances in study cohorts and visualization techniques, are valid and accepted methodological approaches.

Implications for Practice

The outcomes from chapters 3 and 4 describing PC patients in South-Central Appalachia have yielded a wealth of information applicable to the broader population. No revolutionary findings were identified regarding risk factors. However, the known risk factors are not risk factors for the study population. For example, Bosetti et al. (2012) and Carreas-Torres et al. (2017) are cited frequently for their work showing diabetes mellitus, and insulin resistance are risk factors for PC development. However, in this cohort, diabetes mellitus was present in less than half the study population and was not found to significantly affect the stage of disease, length of overall survival, or overall survival status. This is an opportunity for future research. Other regions of the country may have similar relationships with diabetes and PC, suggesting other factors are present in those individuals who develop a sudden and unexpected diabetes diagnosis and subsequent PC. This could lead to a better overall understanding of the

pathophysiology behind PC. Additionally, there may be social determinants of health (SDOH) at play as covariates that in some individuals cause diabetes to be a risk factor and in others not.

Need factors reviewed, based on the Andersen (1968) Behavioral Health Model, such as tobacco abuse, alcohol abuse, obesity, and pancreatitis, are the high-risk variables most associated with adverse outcomes in this example of South-Central Appalachia. The clinical implication is, that clinician understanding of their population and its unique needs and attributes will allow clinical practice to be tailored to the patients in a novel way. For PC patients in South-Central Appalachia, this means focusing on smoking cessation, treating alcohol abuse, and encouraging weight loss. Additional research is needed in this area, but for a disease as lethal as PC, a real glimmer of hope for patients exemplifies how nursing can impact clinical prognosis. Using the knowledge generated by this study, nursing staff (RN or APRN) can develop evidence-based practice recommendations by stratifying resources for newly diagnosed PC based on their risk factors. Nurse-provided resources to help with smoking cessation, maintaining healthy nutrition habits, and even preoperative rehabilitation can positively impact outcomes for appropriate PC patients. These resources can be provided by existing nursing resources, including nurse navigators within the oncology setting and nurse practitioners practicing within medical, radiation, and surgical oncology.

The ability to stratify PC patients has further practice implications. Following 2020, national trends in treating PC shifted. In 2021, newly diagnosed PC patients were encouraged to engage in neoadjuvant, or upfront, systemic chemotherapy – even when the disease was identified early enough for surgical resection. As a result, many (but not all) of the patients in the data used for chapters 3 and 4 who had surgical intervention may not receive surgery before chemotherapy if they were to present to the high-volume PC treatment center today. This trend resulted from prior research suggesting patients who had upfront surgical intervention in some cases did not proceed to systemic therapy; this paradigm shift in treating PC is summarized and defended by Pecorelli et al. (2019). However, the same year, Aziz and colleagues (2019) identified PC patients who received neoadjuvant therapy before surgical resection of their disease had other post-operative issues not previously seen in patients who did not receive cytotoxic treatment first. This study represents a novel way to stratify patients by showing those with a greater risk for disease progression and poor overall survival potential and may aid in treatment decision-making for patients and providers when known high-risk comorbidities exist.

Additional research is needed to determine how to best employ stratification based on the presence of known risk factors and whether this suggests these individuals should have neoadjuvant approaches with systemic therapy or proceed directly to surgery when PC is resectable at the time of diagnosis. Additionally, the findings from this study have affirmed many attributes

in the literature, such as how smoking cessation can improve outcomes even in PC. This and other results from the study provide an opportunity to develop best practices for the population of interest. Similar studies could be easily completed for other populations and for different disease types to contribute to improved care through best practices by establishing a population-specific evidence base: an exciting prospect for PC.

While cancer survivorship is not frequently a concept associated with PC, this dissertation study suggests PC patients who do have a prolonged disease-free survival interval following multi-modal (surgical, systemic, and radiation) treatment, a survivorship care plan that aids patients in avoiding healthcare issues known to reduce survival become even more valuable (Frick et al., 2017). Additional research is needed to understand how high-risk variables associated with adverse PC outcomes impact patients during treatment versus the survivorship period following treatment completion. For example, diabetes was not a significant risk factor for PC outcomes in this dissertation study. However, it is unknown whether there a long-term difference in recurrence-free survival for PC survivors between diabetics and non-diabetics. The same question could be asked of other co-morbidities such as hypertension and heart disease. Because the concept of survivorship is individualized to the patient, additional research into this cohort would help stratify PC survivors into recurrence risk categories and help guide survivorship surveillance.

Finally, the findings from this study support the premise that PC patients receiving care at high-volume PC treatment centers have the best outcomes (Thomas et al., 2022). Given the improved overall mortality rate for the study population (75.5%) versus that of the state of Tennessee (89%), this represents an actual bright spot for healthcare in Appalachia and firmly establishes the intrinsic value of an academic medical center to the community that it serves.

Implications for Policy

Unexpectedly, this study identified that having a primary care provider (PCP) significantly influenced all PC outcomes. It was an assumption established well before data analysis that having a PCP would likely result in a difference in presentation stage, with patients having a PCP identified earlier in the disease process versus those without who would be identified with more advanced disease. While this assumption, based on anecdotal observation, proved to be accurate, the study also revealed that patients with a PCP had a longer overall survival following diagnosis. There are exciting policy implications associated with this finding. While not accounted for during dataset building and cleaning of the data, many of the individuals represented had an advanced practice provider (APP), Nurse Practitioner (NP), or Physician Assistant (PA) listed as their primary care provider. Future studies with this data could return to the charts to determine the nature of the PCP listed. Additional analysis could be conducted to determine if there were any significant differences in outcomes for patients who

see an APP versus a physician as their primary care provider. In a state such as Tennessee, this data would help advocate for full practice authority for PCPs.

In addition, with the passage of the Cures Act in April 2021, Fant et al. (2022) summarize the importance of maintaining collaborative patient-provider partnerships. The Cures Act is a federal mandate requiring patients to have full access to their medical records at a time when patients are increasingly savvy and accessing their records and reviewing standards of care, including cancer treatment, the use and application of new knowledge in diseases such as PC is more important than ever. Translational use of knowledge to provide evidence-based, personalized care is an excellent example of how nurses, APPs, and clinicians of all backgrounds can work towards and maintain collaborative relationships with patients.

Another interesting and unexpected finding was that individuals who lived further from the treating academic medical center had more advanced-stage disease upon presentation and often had a decreased overall 5-year survival. Despite this, no difference in overall survival was identified. Individuals who lived further away (60 and 90-minute drivetime) progressed in their disease faster than those who live closer to the academic center (see Figure 2, Chapter 4 Kaplan Meier curve). This suggests that variables at play are unaccounted for in the current study. Of those patients who live outside of the 30-minute drivetime associated with the metropolitan area surrounding the academic medical center, it would be interesting to show who had a PCP and who did not, and again what

the nature of that PCP was. Presuming at least no significant difference in outcomes whether a PC patient has an APP or a physician as their PCP, this information would support policy efforts to improve PCP access in rural communities, including incentivizing opportunities that offer loan repayment (Scarborough et al. 2016).

Implications for Future Research

A genuinely exciting aspect of this study is its implications for using the combined statistical analysis methodology and geospatial mapping with electronic medical record data for other cancer diagnoses. PC is the subject of this study for the reasons previously described. Still, one of the foremost reasons was that PC is a neglected disease with no representative studies previously conducted on an Appalachian population in the literature. Techniques applied in this study, especially the ArcGIS analysis, could be used with other cancer diagnoses or even non-malignant chronic diseases pervasive in Appalachia, for example, diabetes and obesity. Consider a similar application to congestive heart failure patients treated in the inpatient setting. High-risk variables identified in these patients implicated in hospital readmission increased morbidity, and of course, mortality would have far-reaching implications. The use of ArcGIS data in providing an independent, non-biological variable to understand healthcare access and disease prognosis in congestive heart failure would have a direct economic impact. This attribute helps understand how non-clinical attributes

impact outcomes and provides a valuable continuous data point, dramatically expanding analytic possibilities.

For the PC population itself, future research implications here include studies using state tumor registry data to understand regional differences. State tumor registry PC data could then be used to compare the population in this study with access to a high-volume PC treatment center to the population in west Tennessee, where there is no high-volume pancreas center. Also, including state registry data would improve patient representation, and issues of healthcare disparities between ethnic groups, socio-economic groups, age groups, and individuals with different insurance coverage would be possible. The current study represents an overall homogenous population with a minimum of diversity, given that 89.8% of the study population identified as white.

Finally, much more can be done with the current dataset. Future planned projects include using the ArcGIS tools to forecast PC impact on the study setting based on the existing dataset. The use of ArcGIS to portray PC incidence annually over the study period, rather than in aggregate, to determine if any temporal trends in incidence are identifiable is in progress. The current data could also be used to design a prospective study using the same population and study variables, incorporating a qualitative analysis to add a layer toward understanding health access behaviors from the individual patient perspective. The opportunities presented by this study also extend beyond the study site and even the region of Appalachia. Using the established dataset, joining ongoing

projects designed to understand PC better and identify those at high risk of developing PC, such as the multi-site, Pancreatic Cancer Early Detection Consortium, PROCEED (Simeone, 2021). This is another example of how the research presented in this dissertation is simply a steppingstone for much more.

Broader Implications of the Current Study

The broader implications of this study are as follows. First, this study lends additional evidence to the premise that PC treatment at a high-volume center is ideal (Thomas et al., 2022). This is an essential finding for several reasons. First, high-volume centers are few and far between geographically (Fig. 5, Appendix Chapter 3). Spatial accessibility to these centers is problematic in many areas of the country, and this study demonstrates that spatial accessibility influences outcomes. This finding is evidence that high-volume centers have value for patient outcomes. As these facilities are often academic medical centers, this is an important finding suggesting efforts to support these facilities are well-founded. Next, several novel findings were identified by this study, some of which were unexpected. Most surprisingly, diabetes did not significantly influence PC outcomes in this study and affected less than half of all PC patients. This supports the research effort fundamentally, but for PC, this is inspiring. This represents the potential for improvement in PC care at the fundamental clinical level, returning to primary care and identifying high-risk patients. The knowledge gained from this basic secondary data research has the potential to have an impact on future patient care. Any improvement in survival outcomes that results

will be tremendous for a disease like PC. Coupled with emerging pharmaceutical therapies and the ability to personalize care with somatic and germline genomic attributes, we have the opportunity to see the prognosis for PC improve dramatically in our lifetime. This affirms that despite most PC research being high-level pharmaceutical and genomic research, basic science still has room to impact a better future for PC patients.

Strengths and Limitations

Study limitations include inconsistent documentation of systemic therapy offered and given to the patients represented in the dataset. This information is recorded in a piecemeal, narrative format that prevents logical categorization. This information would be precious in evaluating outcomes between different systemic treatment approaches. The inclusion of this data would require natural language processing abilities that were beyond the scope of this dissertation. The dataset also does not include any genomic data, which would provide a valuable component to understanding both etiology of disease, but also would be advantageous in forecasting future incidence, especially when coupled with cascade testing, testing of first-degree relatives, and results. To complete data analysis, several nonparametric variables required conversion to conduct statistical analysis. This limits the overall interpretation of these results. Following this, all statistical analyses included in this study were bivariate analyses except for the survival analysis (Kaplan Meier and Cox Regression). Controlling for

different co-variables would be valuable in interpreting survival outcomes for the PC patients represented. Finally, as described previously, PCP expressed as a binary yes/no, and the categorization of PCP as an APP or physician was not done. This would be a valuable data point for future analysis, allow for additional research questions, and support specific policy positions.

This study had numerous strengths to balance these weaknesses. First, this study represents a first-of-its-kind presentation of PC patients from South-Central Appalachia. This study is the first to represent Appalachian PC patients at the scale represented, with previous studies limited to much smaller populations (Brotherton & Welton, 2016; Thomas et al., 2022). This study also had convenient and full access to the data, including patient residence data. This level of data access was critical, and the findings included would not have been possible without this access. The use of Andersen's Behavioral Model for Vulnerable Populations was a significant strength in understanding and interpreting the results of the data analysis. This strength will translate well to the translational application of the findings from this study based on the logical categorization of the different factors contributing to healthcare access. Finally, the study enclosed demonstrates room for improvement in the care of PC patients at the clinical level. A literature review reveals a wealth of genomic and pharmaceutical research devoted to PC but a dearth of basic science.

Discussion

In the introduction, there are three specific aims. These aims consist of describing the demographics of PC patients in South-Central Appalachia, understanding healthcare access by assessing healthcare and demographic variables for PC patients over time and space and using ArcGIS to determine if a patient's location is an independent predictor of PC outcomes. The first aim was fully accomplished in the second manuscript, chapter 3. Chapters 3 and 4 partially achieved the second aim, but trends over time were not assessed. This remains for a future study opportunity, including using annualized data to forecast incidence and outcomes using tools available in ArcGIS. Finally, the third aim of determining whether the patient's location is an independent predictor of PC outcomes was also fully accomplished.

The broader implications of this study were explored in the introduction and are repeated here in chapter five. All five implications were either directly addressed by the current research or have the potential to influence or inspire future work using outcomes from this study. The introduction stated four assumptions. The first assumption was that individuals living further from the high-volume treatment center would have reduced access to primary care. This assumption did not hold to be valid once the data were analyzed, and this would not have been able to be fully explored without the methodological approach taken using inferential statistics and ArcGIS. The second assumption was that individuals in the study living further from the high-volume center would present

with more advanced-stage disease. This assumption was proven correct by manuscripts two and three (chapters 3 and 4). The third assumption that individuals with inadequate insurance coverage would present with more advanced-stage disease and have worse outcomes was also correct. Finally, the assumption that individuals with multiple comorbidities would have worse outcomes was also proven to be accurate. Potential remains for future multivariate analysis.

Manuscripts two and three successfully answered all four research questions in the introduction. Chapter 2's first manuscript established a foundational basis for describing PC risks, predispositions, incidence, and prognosis. In the end, the combination of the three manuscripts successfully explored the trajectory of PC, beginning with an overall view and then shifting to a more detailed description of PC for a specific population. The discussion of future practice, policy, and research implications here shows the potential for exciting translational work and additional research building from the knowledge produced within these pages.

Contribution to Nursing

The dissertation study contained within these pages makes several contributions to Nursing as both a science and a discipline. From the large-scale perspective, this study contributes new knowledge to nursing science. This study achieved the aims set forth and described previously by describing the PC

population of South-Central Appalachia, examining how known risk-factors influence PC outcomes, and demonstrating the role of spatial location and proximity to the healthcare center influenced PC outcomes. This knowledge will also be a novel contribution to the larger nursing literature as well as the PC literature, which, the literature review has demonstrated does not contain many contributions from the nursing perspective.

The findings from this study represent a ripe opportunity for future nursing interventions including evidence-based practice solutions for PC patients and quality improvement projects. Nurse navigation has been referenced on several occasions in this review, and data collected from this study could be used to demonstrate the efficacy of nurse navigation on improving PC outcomes. During the study period, a formal nurse navigation program for PC patients was established. Outcome data from this study could be used to assess nurse PC outcomes in the years represented prior to the nurse navigation service line, and then following establishment of this role.

Finally, this dissertation and the methodology used to accomplish the aims described represents a valuable contribution to nursing science. The methodology of incorporating GIS methods and data into quantitative research is a powerful methodological approach for future nursing research studies to incorporate. Not only is this an approachable methodological technique for nurse scientists to consider, but it also is a technique that lends itself to multi-disciplinary team science as demonstrated by the study from Hutson et al.

(2020). This is an important concept as team science, multi-disciplinary approaches are becoming more common and are an excellent opportunity for nurse scientists to become part of the larger scientific literature in numerous subjects beyond oncology research.

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VITA

Andrew Ward is a native of Upper East Tennessee and spent his formative years as a son of Appalachia in East Tennessee and Western North Carolina. Following high school, Andrew received the Congress-Bundestag scholarship to study abroad in Germany before entering higher education. Andrew received his undergraduate degree from The University of Tennessee and a subsequent master's degree from the University of Arkansas in Anthropology, focusing on physical and forensic Anthropology. Motivated by this experience, Andrew chose to explore a different path academically. He returned to his native East Tennessee, enrolled in the master's entry program in the College of Nursing at The University of Tennessee, and received his Master of Science in Nursing as a Family Nurse Practitioner. Andrew spent the next five years in primary care as a Nurse Practitioner for medically underserved and underrepresented individuals residing in South-Central Appalachia. Andrew then transitioned practice to Oncology and has practiced with the division of surgical oncology for more than a decade seeing patients from diagnosis through survivorship. After graduation, Andrew will continue his clinical practice with oncology patients at The University of Tennessee and will continue his academic and research interest with the College of Nursing as research faculty with dual appointment between the University of Tennessee and the University of Tennessee Medical Center.