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Pathopoiesis Mechanism of Smoking and Shared Genes in Pancreatic Cancer

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Walden University
2017

Abstract

Pathopoiesis Mechanism of Smoking and Shared Genes in Pancreatic Cancer

by

Ulysses Labilles

DMD, Centro Escolar University, 1986

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health, Epidemiology

Walden University

November 2017

Abstract

Pancreatic cancer (PC) remains a significant, unresolved issue because of its complex genetic blueprint and lack of reliable detection markers. The purpose of this study was to examine the possible correlation between tobacco use, gender, and age in the etiopathogenesis of PC and other cancer types with a shared-gene association (CTSG-A). The unified paradigm of cancer causation was used to understand the pathopoiesis mechanism of smoking and shared genes in PC. A cross-sectional study was performed using secondary data from the cancer survivorship module of the 2014 Behavioral Risk Factor Surveillance System survey. Results of ordinal logistic regression analyses indicated no correlation between smoking and prevalence of PC and CTSG-A, but gender and age were significant predictors. Gender has a statistically significant effect on the prediction of PC/ CTSG-A induction and promotion. Increased probability of developing the disease was found as the person reach the age between 62 and 69 years of age. Findings may enhance the understanding of environmental, genetic, and biodemographic interactions in disease evolution (induction, promotion, and expression periods). Findings may also be used to promote population health and improve health behaviors for individuals in vulnerable, high-risk groups.

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Dedication

A night before my youngest brother passed away, he said, "Promise me that you will go back to school, and someday take on a research project that could make a difference to individuals diagnosed with this very painful disease." He passed away in 2007 of pancreatic cancer, a few weeks before his 40th birthday, and 3 months before the first birthday of his only daughter. In December 2012, as a promise to my brother, I enrolled in the Public Health Ph.D. program specializing in epidemiology. When a sad or tragic event happens, we have three choices. We can let this event define us, let it destroy us, or let it strengthen us. For somebody who is over 50 years old like me, going back to school is sometimes misconstrued as a dream too high to reach. To be given an equal chance to have a better education is not about to a sense of pride, but about making a difference for others who have nothing but hope. The courage to face any obstacles is an important component of positive social change.

In Texas, we believe in winning big as the American dream. My dream is that everyone, not just my family and me, will have a better understanding of the complexity of pancreatic carcinogenesis after reading this dissertation. Words cannot express my gratitude and love throughout this journey. I would like to dedicate this dissertation to my brother, Rey; his daughter, Leighna; my daughter, Abigail; and my boys, Reighben, Duanne, and Dwight.

Acknowledgments

I started this journey by listening to the iTunesU Public Health 241 Spring 2012 lectures by Dr. Nicholas P. Jewell of UC Berkeley. Many people have contributed to this dissertation, and I owe them my sincere gratitude for making this endeavor possible. I would like to thank Dr. Precilla Belin for her guidance, understanding, and patience during this process. She encouraged me to grow as scholar/practitioner, and she placed an indelible mark on my intellectual development. I would also like to thank my former professor, Dr. Wen-Hung Kuo, who was a member of my committee for his input, valuable discussions, accessibility, and mentorship since 2013. The insightful comments and constructive criticisms of Dr. LaToya Johnson, who served in the role of university reviewer, helped me focus on my ideas. No one can achieve their dreams alone. I have the strength that my daughter provided, as well as the sparks of knowledge I got from Dr. Jewell and the scholarly footprints of researchers who helped me shape this dissertation and justified the positive social change that could enhance the quality of life for those fighting pancreatic cancer. Lastly, I would like to acknowledge President Barack Obama who reminded me that there is always hope. On his letter dated June 16, 2016, he noted how the experience we share in experiencing grief and hardship of losing a family member made him forge a future free from cancer in all its forms. He highlighted the mission statement of the Moonshot initiative in accelerating progress toward prevention, treatment, and cure to spare more people the heartbreak cancer causes.

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Chapter 1: Introduction to the Study

To raise new questions, new possibilities, to regard old problems from a new angle requires creative imagination and marks the real advance in science (Einstein & Infeld, 1938, p. 92). Pancreatic cancer (PC) at the start of the 21st century continues to be a vital unresolved health problem, remaining as one of the deadliest human cancers. Although genetic changes can be either somatic or hereditary, described as de novo (new), PC does not arise de novo (Maitra & Hruban, 2008), but rather initiated by a probable gene mutation such as p16/CDKN2A that results to debilitating metabolic effects of uncontrolled growth. The five-year survival rate of less than 5% of PC is a statistic that remains constant for many years (Garcia et al., 2007; Hidalgo, 2010; Makohon-Moore, Brosnan, & Iacobuzio-Donahue, 2013). Hoeijmakers (2009) stated that the damage to the DNA is the causality of the development of PC, and continued inquiry is paramount to understand the principles of its cancer biology. Zakharova, Karmazanovsky, and Egorov (2012) found that the minor populations of cells with stem-like properties had been identified and appear responsible for the development and progression of pancreatic cancer. According to Hruban Canto, Goggins, Schulick, and Klein (2010), although some of the aggregation of PC arises from environmental factors such as tobacco use, aggregation of the disease in families could be due to chance and genetics.

There are three ways that DNA can be mutated: inherited mutation in the context of genetic predisposition or susceptibility, DNA mutation caused by behavioral risk factors, and DNA damaged by chance (Couch et al., 2007; Irigaray et al., 2007; Jones et

al., 2009). Even if an individual has an inherited syndrome or inherited predisposition, a person with one good copy of the cancer-associated gene may or may not develop the disease (Suter, 2015). Given the assumption that a disease is caused by a factor that can be controlled, exploring the relationship between modifiable health behaviors such as smoking and family cancer history (FCH), cancer predisposition genes (CPG) or shared genes was a legitimate endeavor. In this study, genetic syndromes associated with PC were interchangeably referred to as FCH, CPG, or shared genes. Understanding of the biology of PC has progressed over the years, including advances in patient management. According to Vincent, Herman, Schulick, Hruban, and Goggins (2011), the evidence is starting to show that first-degree screening relatives of individuals with several family members affected by PC can identify noninvasive precursors of this lethal disease. Vincent et al. demonstrated the incidence of and the number of deaths caused by pancreatic tumors had been gradually rising, even as incidence and mortality of other common cancers have been declining. The poor response to most chemotherapeutic agents among patients with advanced unresectable PC (Vincent et al., 2011) highlights the need for more effective control of tumor initiation and metastasis, and for a better understanding of the evolutionary framework of the disease.

Exploring the Darwinian nature of PC could lead to improvement in conventional therapies. Vincent et al. (2011) justified the significance of understanding the biological mechanisms contributing to the development and progression of pancreatic tumors. Klein et al. (2004) highlighted the importance of quantification of the risk of individuals with shared genes as a basis for cancer risk screening and counseling. In this cross-sectional

study, the quantification of PC risk among Behavioral Risk Factor Surveillance Survey

(BRFSS) participants diagnosed with the disease supported the assumption of increased

risk in association with shared genes and shared environmental factors such as smoking.

Given Blackford et al.'s (2009) findings regarding the nonspecific DNA damage caused

by tobacco carcinogens, I examined the correlation between tobacco carcinogen-related

mutations, inherited cancer predisposition, and new cases of pancreatic cancer. The social

change implications of this study depended on the success of quantifying the association

between smoking and CPG, highlighting the importance of tobacco-use cessation as a

lifestyle and health-enhancing behavioral change. Although findings may not have

indicated an association between tobacco use and CPG in the development and

progression of PC, including gender and age, the study amplified the need for smoking

cessation programs and cancer-specific profiles.

Background

Tersmette et al. (2001) and Reznik, Hendifar, and Tuli (2015) examined the risk

of developing PC among first-degree relatives in families with the disease using the

National Familial Pancreas Tumor Registry (NFPTR). Hruban et al. (2010) confirm the

elevated risk level of both pancreatic and extrapancreatic malignancies to individuals

with a family history of PC. Although the genetic basis of more than 80% of the

clustering of pancreatic cancer in families remains unknown, Hruban et al. addressed the

significance of the resultant flood of information that could be generated by investigators

at Johns Hopkins University in sequencing candidate familial pancreatic cancer genes.

The findings strengthened the NFPTR through aggregation of data from international

screening and surveillance by a consortium of 25 countries. Likewise, the 2013 study by

Canto et al. supported the importance of screening, surveillance, and management of

high-risk individuals with an inherited predisposition to PC. Reznik et al. (2015) also

discussed the future directions and usefulness of screening for individuals with familial

pancreatic cancer. Similarly, Bartsch, Gress, and Langer (2012); Brand et al. (2007);

Canto et al. (2013); and Klein (2012) discussed the practicality of screening swirled on

individuals who are carriers of a mutation in an established high-penetrance pancreatic

ductal adenocarcinoma (PDAC) susceptible genes—BRCA2 (BReast CAncer gene two)

and PALB2 (Partner and Localizer of BRCA2).

Prokopczyk et al. (2002) and Ding et al. (2008) investigated the combined

causality of non-tobacco-related mutagenic risk factors such as the inherited

predisposition to cancer that may share mutagenic properties with the tobacco mutagens.

Debates over the current knowledge of modifiable risk factors, such as smoking, tend to

dominate in the likelihood of increased probability of developing the disease. Schulte et

al. (2014) elaborated the smoking component primarily relevant to pancreatic cancer risk

(PCR). After analyzing data from the Queensland Pancreatic Cancer Study, the result

provided the evidence that in addition to dose effect of tobacco use, the smoking pattern

may affect PCR. The body of knowledge given by these researchers justifies the purpose

of this dissertation in examining the association between smoking and the initiation and

progression of the disease in an individual with FCH. Breitkopf et al. (2012) confirmed

the importance of addressing behavioral and genetic risk factors for PC, parallel to the

association of gender and age, supporting the value of this dissertation in addressing the dearth of existing data on the etiopathogenesis of the disease.

Current State of Understanding

The pancreatic cancer putative cell of origin remains elusive despite the progressive increase in the understanding of pancreatic carcinogenesis from intensive histologic and genomic research (Maitra & Hruban, 2008). Patients diagnosed with PC stay asymptomatic until the progression of the disease propelled at an advanced stage, making PC stand out among the most lethal malignancies (Braat, Bruno, Kuipers, & Peppelenbosch 2012; Siegel, Naishadham, & Jemal, 2012). Moreover, this disease often mimics other benign conditions, making this disease one of the most challenging cancers to detect and treat (Lowenfels & Maisonneuve, 2006). Tobacco use remains the most well-established risk factor for PC (Maisonneuve & Lowenfels, 2015), and since the 1970s, smoking cessation has become the primary tool for reducing the risk of the disease. From 2008 to the present, investigators such as Petersen et al. (2010) focused on mapping the pancreatic cancer genome and identified common susceptibility loci for PC that warrant follow-up studies. The primary reasons behind poor prognosis are early metastasis, chemo resistance, and late clinical outcomes, making PC the fourth leading cause of cancer-related death globally (Malhotra, Ahn, & Bloomston, 2015). Given the heterogeneous nature of PC etiology with an extensive variety of modifications (Thomas et al., 2014), the pancreatic tumor genome sequencing provides a path-breaking opportunity in mapping smoking-related mutational patterns.

Accumulating evidence indicated that carcinogenic tobacco compound contributes to the development of pancreatic cancer (Pandol, Apte, Wilson, Gukovskaya, & Edderkaoui, 2012). Blackford et al. (2009) argued that smokers could develop a bigger number of mutations than nonsmokers, doubling the risks that record for 20 to 25% of pancreatic cancers. The types and mutational patterns observed among smokers in Blackford et al.'s study gave additional insights on the pathopoiesis component by which cigarette smoking causes PC induction and promotion. Parallel to Blackford et al.'s conclusion on the impact of tobacco use in increasing the risk of pancreatic growth through components other than genetic mutations, Porta et al. (2009) found that tobacco smoking increases the risk of PC through events other than Kras mutations. After the researchers had evaluated all of the available types of epidemiological and clinical studies on the occurrence of V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations in human adenocarcinomas in correlation to smoking, the results supported the hypothesis that tobacco use influences the risk of PC.

Problem Statement

Pancreatic cancer has been estimated to have higher mortality rates, with an economic encumbrance of $4.9 billion annually (Pandol et al., 2012). The prognosis of pancreatic cancer remains dismal despite the substantial progress in the understanding of PC biology. Germline mutation makes up 5% to 10% of all cancers, and of the germline gene mutations that have been identified to increase PC risk, mutations in BRCA2 account for up to 17% of familial pancreatic cancer (FPC) kindreds (Murphy et al., 2002; Hahn et al., 2003; Couch et al., 2007). As genomic sequencing technologies have

decreased in cost and become more commonplace, there has been much to learn

regarding differential sensitivities of various DNA damage response (DDR) gene

mutations, such as somatic versus germline and new mechanisms of treatment resistance

(Carnevale & Ashworth, 2015). Although genetics may play a role in disease

development, the procarcinogenic effect of smoking is considered the precursor to the

development and progression of pancreatic cancer according to Vincent et al. (2011).

Both Blackford et al. (2009) and Schulte et al. (2014) highlighted the association of

smoking pattern in the increased risk of the disease. Although Schulte et al. confirmed the

magnitude of dose effect of smoking to the disease, Blackford et al. failed to establish a

characteristic profile of the number of tobacco carcinogen-related mutations within the

pancreas (tail vs. head), tumor grade, patient's age, sex, margin status, and stage.

Although the treatment combinations of surgery, radiotherapy, and chemotherapy could

improve the chance of survival and quality of life, continued research in establishing a

unique pattern on the pathobiology of PC malignancy among patients who have a history

of smoking and shared genes is warranted.

Given the evidence that PC, like most human cancers, contains multiple

mutations, continued research is needed to advance the understanding of the essential

principles of its cancer biology (Hoeijmakers, 2009). Although the Darwinian nature of

PC makes the prediction of its evolution virtually impossible (Lennon et al., 2014),

smoking often has a multiplicative increase in PC risk when combined with other risk

factors such as alcohol, recent onset diabetes, and family history (Jansen, Tan, &

Petersen, 2015; Schenk et al., 2001). Carcinogens from tobacco such as N-nitrosamines,

benzo(a)pyrene, polycyclic aromatic hydrocarbons, A-napthylamine, methylfluoranthenes, and arylamines are capable of forming DNA adducts that increase the risk of somatic mutations and PC (Jansen et al., 2015; Suwan-ampai, Navas-Acien, Strickland, & Agnew, 2009; Vrieling et al., 2010). In addition to an increasing amount of research regarding dynamic epigenetic processes and their role in gene regulation (Jansen et al., 2015), past and present epidemiologic studies such as Yang et al. (2012) indicated a significant interaction between smoking and cytotoxic T-lymphocyte-associated protein on the risk of PC.

Jansen et al. (2015) underscored the significance of genetic data that can assist in identifying individuals at high risk of developing PC, which confirms the need for new statistical and epidemiological methods to pinpoint the responsible genetic variants and their interaction with modifiable risk factors. Tobacco use is a modifiable risk factor that has been studied extensively (Iodice, Gandini, Maisonneuve, & Lowenfels, 2008). Taking into account the gene-environment interaction with modifiable risk factors such as tobacco use is the cogent step to understanding the epidemiology and pathometry of PC. The unique contribution of this dissertation to the current body of knowledge involved examining the links between tobacco use, gender, age, PC, and shared genes. This dissertation could promote population health, and lessons learned could reshape the current understanding of cancer epidemiology by providing the scientific justification for the implementation of screening, surveillance, and education programs. The outcome of this dissertation would fit into the practical intervention approach of adopting a healthy lifestyle such as smoking cessation as part of positive, meaningful social change to

improve prognosis and quality of life during PC progression. Like the Pancreatic Cancer Detection Consortium (PCDC), the principal intent of this dissertation was in response to the Recalcitrant Cancer Act, signed into law on January 2, 2013, after strong bipartisan support for President Barack Obama. The outcome of this study could support the 21st-century thinking that underscores the influence of modifiable risk factors in relation to healthy lifestyle choices in lowering the risk of developing pancreatic cancer. The mechanism through which the role of smoking in augmenting the development or accelerating the progression of PC to individuals with FCH, CPG, or shared genes needs a well-grounded inquiry for new complementary/alternative research direction that will underpin the existing body of knowledge. In response to the need to enhance the understanding of PC epidemiology, this dissertation will address the gap in exploring the interaction between shared environmental factors (tobacco use) and shared genes, as well as the role of gender and age as explanatory variables.

Purpose of the Study

PC is a complex and highly lethal disease, best treated in a multidisciplinary setting. The grim survival statistics of PC justify the intent of this dissertation to establish clarity about the pathopoiesis mechanism of tobacco use and CPG or its combined role in the etiopathogenesis of the disease. There are numerous studies on the association of relevant risk factors for PC, but there are limited studies linking smoking level to CPG or FCH. Schottenfeld and Fraumeni (2006) and Silverman et al. (1994) asserted that smoking exhibits its biologic effects on both early and later stages of the carcinogenic process. The purpose of this dissertation was to establish clarity on the role of tobacco

use in the development of PC among individuals with FCH, cancer predisposition gene (CPG), or shared genes. Because the size of the primary lesion has a correlation with long-term survival, the innate metastatic propensity of this disease needs further study addressing the behavior, prevention, and mechanisms associated with pancreatic cancer risk (Chari et al., 2015; Perera & Bardeesy, 2015). Although it is important to treat a complex and highly lethal disease like PC in a multidisciplinary setting, Wolfgang et al. (2013) asserted that the prevention of an invasive PC is dependent on the improvements in the management of cystic pancreatic lesions.

Research Questions

Pancreatic cancer and other cancers found to have a shared-gene association (S-GA) were the dependent variables, and smoking status, age, and gender were the independent variables; this study addressed the following research questions (RQs) and hypotheses:

RQ1: Is cigarette smoking associated with the etiopathogenesis of pancreatic cancer and cancer types with shared gene association (CTSG-A)?

H_{01}: Smoking level has no correlation with prevalence of PC and CTSG-A.

H_1: Smoking can increase the risk of PC and CTSG-A.

RQ2: Is there a relationship between the combined role of age and gender in the etiopathogenesis of PC and CTSG-A?

H_{02}: Age and gender have no correlation with prevalence of PC and CTSG-A.

H_2: Age and gender are correlated with the prevalence of PC and CTSG-A.

Chapter 3 provides a more detailed discussion of the objectives, research questions, hypotheses, and analysis plan.

Theoretical Basis for the Study

To properly frame the hypothesis that tobacco use, gender, and age in combination with inherited mutation could increase the risk of developing PC and CTS-GA, a metatheory was appropriate to unriddle the axiom of biologic synergism and the link of a causal modifiable risk factor. Based on Rothman's (1986) notion of epidemiologic interaction, the biologic synergism explored in this dissertation was the sufficient cause of tobacco use (A) and cancer predisposition gene or FCH (B); if both are present, there is an increased risk of PC. Although the sufficient cause paradigm could also help support a working hypothesis that individuals with inherited mutations have a higher risk for the disease without A, the presence of A or act in combination with B could mean a probable higher cause of malignancy. On the other hand, removal of A implies that the probable additional mutations caused by exposure to A could eliminate the sufficient cause of A in the etiopathogenesis pathopoiesis (see Figure 1).

Knudson's two-hit theory of cancer causation may be appropriate in explaining the pathopoiesis mechanism involved in FCH. However, the Unified Paradigm of Cancer Causation (UPCC) as the proposed metatheory in this dissertation could provide arguments on the positive association (synergism) between tobacco use and FCH, giving more clarity to Rothman's notion of epidemiologic interaction or the paradigm of sufficient cause. UPCC is a composite construct of the germ theory and the somatic mutation theory of carcinogenesis (SMT) in combination with the traditional or

Darwinian evolutionary system (Greaves & Maley, 2012), Knudson's two-hit theory

(Hermanowicz, 2015), genome theory, Darwinian theory of social change (Richerson &

Boyd, 2000), and the multi-level biologic, social integrative construct (MBASIC). The

theoretical cocktail of UPCC could interlock new insights on tumor initiation, metastases

diagnostic, and treatment strategies.
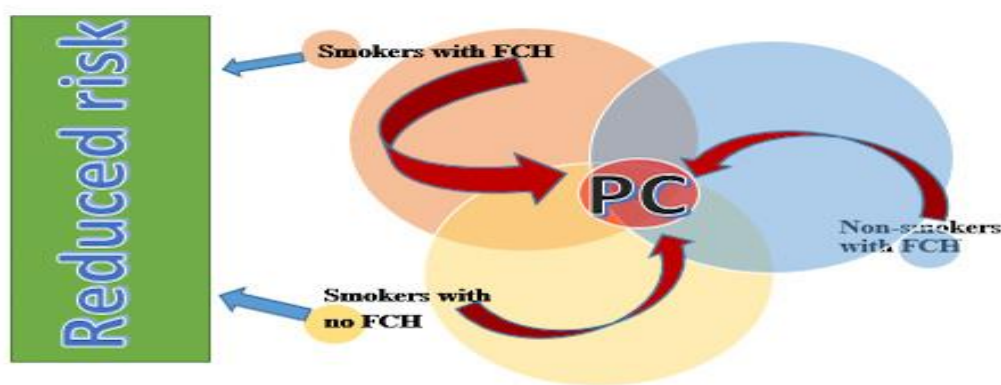
Figure 1. Component cause model for the causes of hypothetical pathopoiesis mechanism
of smoking and family cancer history in the etiopathogenesis of pancreatic cancer.

The germ theory of disease of the 20th century needs to be in the context of 21st

century medicine (Whitcomb, 2014) and part of a metatheory that will classify patients

based on a risk factor or a combination of factors (e.g., smoking, gender, age) that could

contribute to the existing knowledge of PC etiology rather than its symptoms and

complications. Although traditional evolutionary theory could help the understanding of

pancreatic tumor growth at the molecular level (Aktipis, Boddy, Gatenby, Brown, &

Maley, 2013), the genome theory of cancer evolution (Vogelstein et al., 2013) could help

explain the direction of development and pattern of progression of the disease. Cancer of

the pancreas is a genetic disease, and MBASIC could help explain its Darwinian

character and link the correlation of tobacco use and family cancer history. According to

Lynch and Rebbeck (2013), MBASIC allows researchers from the fields of public health,

health policy, epidemiology, biology, clinical medicine, prevention, behavioral sciences,

sociology, and others to test hypotheses of interest. MBASIC aided in the study design,

guided the development of statistical or mechanistic models to examine the covariates,

and positioned the results of this study for improved intervention, translation, and

implementation.

<p align="center">**Nature of the Study**</p>

Assessment of lifetime smoking history selected through random stratification

from the core sections and cancer survivorship module of the 2014 BRFSS data sets was

not only a valuable instrument for this study but also for the future development of the

Expanded BRFSS. The key variables in this dissertation were cancer types from the

BRFSS cancer survivorship module (outcome), and the core section on tobacco use,

gender, and age (predictors). The intent of this study was to examine the association

between smoking, gender, age, PC, and shared genes. Popular study designs are subject

to various biases that include social desirability, recall, and selection bias. Despite the

weaknesses of secondary data and cross-sectional studies, multiple outcomes and

exposures can be explored using a cross-sectional design.

The argument on the influence of tobacco consumption on individuals with shared

genes and calculating prevalence proportion, the positive and negative predictive values

of the regression models were assessed to determine the statistical significance of the

independent variables (smoking status, gender, age) in the induction and progression of PC. The ordinal logistic model was used to consider possible correlation. Secondary data from the 2014 BRFSS were recoded and randomized using the Statistical Package for the Social Sciences (SPSS).

Definitions

BRCA2: BReast CAncer Gene 2, the tumor suppressor gene associated with hereditary predisposition to pancreatic, breast, ovarian, and other cancers (Cassidy, Liau & Venkitaraman, 2014).

Clonal mutation: A mutation that exists in the vast majority of neoplastic cells within a tumor (Vogelstein et al., 2013).

Darwinian model: A theory used to explain that the genetic variation introduced continually into the population via stochastic mutational events and that those cell clones that happen to acquire alleles conferring proliferative and/or survival advantages become overrepresented via a process of purifying selection (Valastyan & Weinberg, 2011).

De novo: An alteration/mutation in a gene that is present for the first time in one family member as a result of a mutation in a germ cell of one of the parents or in the fertilized egg itself (Pagon et al., 2016).

Driver gene: A gene that contains driver gene mutations (Mut-Driver gene) expressed aberrantly in a fashion that confers a selective growth advantage (Epi-Driver gene).

Epigenetic: Denoting processes by which heritable modifications in gene function occur without a change in the sequence of the DNA (Spraycar, 1995).

Etiopathogenesis: A portmanteau of etiopathology and genesis; the cause and development of a disease or abnormal condition (Merriam-Webster, n.d.).

Family cancer history (FCH): Familial pancreatic cancer referred to in this study simply as family cancer history (FCH), cancer predisposition genes (CPG), or shared genes—elaborating on the known genetic syndromes (Rustgi, 2014), and germline mutations such as BRCA2 (Grant et al., 2015).

Gene-environment interaction: In genetic epidemiology, genetic factors that confer susceptibility or resistance to pancreatic cancer in a particular environment (Khoury, Davis, Gwinn, Lindegren, & Yoon, 2005; Willett, 2002).

Genetic heterogeneity: The character of a phenotype produced by diverse mechanisms that can be distinguished by special methods such as linkage analysis but are ordinarily indistinguishable.

Genetic polymorphism: The occurrence in the same population of two or more alleles at one locus, each with appreciable frequency (Cavalli-Sforza & Bodmer, 1971).

Genome theory: A model used to guide the understanding of timing occurrence of genetic events in pancreatic carcinogenesis and progression (Makohon-Moore et al., 2013).

Germline genome: An individual's genome as inherited from his or her parents (Vogelstein et al., 2013).

Germ theory of disease: In the context of the 21st century, a framework in which the number of variants resulting in disease equals one (Whitcomb, 2014).

Inherited cancer predisposition: A means to identify genes that may have significant normal roles in the control of growth and differentiation, and which when faulty can predispose to malignancy (Ponder, 1991).

KRAS (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog): One of a class of genes known as oncogenes, which when mutated have the potential to cause normal cells to become cancerous (Kranenburg, 2005).

Latency period: The delay between a cause and its effect, or the time between causal factors and diagnosis (Spraycar, 1995).

Metatheory: The integration of various theories (Anchin, 2008; Ritzer, 1988).

Multilevel biologic and social integrative construct (MBASIC): A model that guides transdisciplinary collaborations to maximize the value of multilevel studies for clinical and public health activities, and to integrate macro environment and individual factors with biology (Lynch & Rebbeck, 2013).

National familial pancreas tumor registry (NFPTR): A research registry established at Johns Hopkins University in 1994 (Shi, Hruban, & Klein, 2009).

PALB2 (Partner and Localizer of BRCA2): A pancreatic cancer susceptibility gene; PALB2 mutations occur in patients with familial pancreatic cancer (Jones et al., 2009).

Pancreatic cancer (PC): The predominant histologic type of cancer in sporadic and familial cancer of the pancreas estimated to become the second leading cause of cancer death in the United States by 2020 (Rahib et al., 2014).

Pancreatic ductal adenocarcinoma (PDAC): Referred in this study as pancreatic cancer (PC), representing the fourth leading cause of cancer mortality worldwide, with an incidence of approximately 217,000 new cases each year nearly matched by 213,000 deaths (Parkin, Bray, & Devesa, 2001).

Pathometry: The determination of the proportionate number of individuals affected with a certain disease at a given time, and of the conditions leading to an increase or decrease in number (Stedman, 2012).

Pathopoiesis: The tendency of an individual to become ill; the mode of production of disease.

Postmodernism: A reaction to the assumed certainty of scientific or objective efforts to explain reality (Stringer, 2014).

Subclonal mutation: A mutation that exists in only a subset of the neoplastic cells within a tumor (Vogelstein et al., 2013).

Susceptibility gene: A gene mutation that increases an individual's susceptibility or predisposition to a particular disease or disorder.

Tobacco use: A modifiable risk factor associated consistently with a twofold increased PC risk (Jansen et al., 2015).

Traditional evolutionary theory: A model explaining evolutionary processes that drive cancer progression; the model helps in understanding tumor growth dynamics to narrow the search for specific mutations that drive different aspects of the disease (Rodriguez-Brenes, Komarova, & Wodarz, 2013).

Tumor suppressor gene: A gene that when inactivated by mutation increases the selective growth advantage of the cell in which it resides (Vogelstein et al., 2013).

Assumptions, Limitations, Scope, and Delimitations

Assumptions

By the year 2020, PC is estimated to become the second leading cause of cancer death in the United States (Chari et al., 2015). Tobacco use may be not only a cancer-causing agent but also a lifestyle-related factor associated with the etiopathogenesis of the disease. Familial pancreatic cancer is thought to be genetically heterogeneous (Zhen et al., 2015), and other inherited mutations are referred in this dissertation as FCH or CPG. All calculations were conducted under the assumption of the association of smoking, gender, and age to individuals with FCH, or the synergism of these factors in the initiation of pancreatic cancer. Yes/no P16(CDKN2A), PRSS1, BRCA1, STK11/LKB genes among participants with FCH, or smoking history as the binary outcome, was explored in correlation with the disease prevalence. The probability of developing pancreatic cancer is virtually impossible to tell. Therefore, it is important to examine the pathopoiesis mechanism of smoking as a lifestyle-related factor or modifiable risk factor in correlation with gender, age, and CPG in the development and progression of pancreatic cancer.

Scope and Delimitations

The occurrence of PC/CTS-GA under the defined combined role of risk factors in this dissertation was sparse or rarely discussed in previous research. Hassan et al. (2007) asserted the need for further assessment of the synergistic interaction between smoking

and diabetes, and positive family history of pancreatic cancer in other large-scale epidemiological studies of different populations, in men and women separately. Gender and age were included in the statistical analysis to establish connections at a single point in time, in addition to smoking lifetime history or its combined role in the prevalence of PC and CTSG-A, statistical adjustment through age post-stratification (<51, 52-69, 70>) to weight for probable selection bias. Reported age of onset for familial pancreatic cancer (FPC) collated from previous investigations was 52-69 years (Norris et al., 2015). In the current study, gender, race/ethnicity, and age were considered for statistical analysis to assess differences in induction and promotion of PC.

The sampling frame of this study included randomly selected data from the 2014 BRFSS. To achieve generalization, G*Power was used to establish sample size. If the suggested sample size failed the ordinal logistic regression assumptions, the remaining sample after data cleaning was used. Producing well-grounded evidence would contribute to the mission of the source of the secondary data. Emphasizing the impact of modifiable or lifestyle risk factors such as smoking in the induction and promotion of PC may promote not only positive social change but also future studies in establishing a national or international consortium for PC to develop a risk model for early detection of the disease (Hassan et al., 2007).

Limitations

Given the time involved and other challenges in establishing institutional collaboration between Walden University and the Johns Hopkins University National Familial Pancreas Tumor Registry (NFPTR), the 2014 BRFSS data sets were used in this

study. Limitations of secondary data include missing data and reusing existing data sets from previous studies. Although it was important to be aware of ethical issues and weaknesses of using secondary data, following the minimum standards of preparing the 2014 BRFSS Module for analysis was critical to the quality of this study.

Significance of the Study

By the year 2030, it is projected that PC will be the second leading cause of cancer death after lung cancer among the major types of cancer (Rahib et al. 2014). The outcome of this study would provide valuable insights into the etiopathogenesis of PC and CTS-GA, as well as the possible recognition of the probable unique pattern of PC malignancy among defined age groups, between men and women, in correlation to the modification effect of smoking to CPG, or its combined impact. Additional understanding of the pathopoiesis dynamics of smoking status, gender, and age in individuals with CPG in the induction and promotion of PC could help promote pre- and post behavioral diagnosis change. This study may assist in developing a novel patient management approach to accurately assess the disease burden under the lens of public health and modern epidemiology.

Variability of previous exposures and cumulative effects of smoking, and prevalence patterns among defined age groups between men and women in association with individuals with CPG versus nonsmokers with CPG could explain the difference in latency periods and degrees of pancreatic cancer progression. Exploring the combined arbitrary role of smoking and CPG in the progression of PC may confirm the importance of addressing the need for fostering behavioral change by adopting healthy habits among

high-risk individuals. Moreover, this study could provide further insights into behavior, prevention, and mechanisms associated with PC risk. Although the procarcinogenic effects of tobacco use on the pancreas are inadequately studied (Pandol et al., 2012), closing the gap in knowledge continuity in the understanding of PC epidemiology regarding the association between smoking and shared genes that could impose comorbid conditions was critical to the advancement of efficient clinical practice. The focus of most research in PC epidemiology is on the improved understanding of risk factors in association with clinical treatment to alter the expression or final stage of the disease. Following the blueprint of public health intervention, this study focused on understanding the interaction between biologic, individual, and microenvironmental factors in the induction and promotion of PC. The outcome of this study may justify the importance of behavioral change.

Positive Social Change Emerging from the Study

The commonality of modernism and 21st century thinking (postmodernism) is the goal of living the highest quality of life. The greatest challenge of this study was to improve the outcome of those diagnosed with PC and CTSG-A known to have increased risk of extrapancreatic malignancies. Patients diagnosed with PC have a poor prognosis of 28% 1-year survival rate, and 4-7% 5-year survival rate (American Cancer Society, 2015). The only way to stop the fear after being diagnosed with PC is by managing emotional issues and social concerns. People may sometimes struggle with changes in their social roles or situation, but high-risk individuals have a choice to make lifestyle changes. The 21st century thinking underscores the noteworthiness of making healthy

lifestyle changes that affect not only the risk of developing the disease but also the ability to function independently in later life. The 21st century approach to advancing the vision for prevention requires innovative steps on integration and a comprehensive way of promoting public health. Part of creative actions is accepting the significance of social change in the sphere of enhanced quality of life. Focusing on the impact of cigarette smoking as a modifiable risk factor that promotes PC and CTSG-A rather than initiates it may amplify the importance of behavioral change promoted through health care policy changes. According to a report on recommendations of the Task Force on Community Preventive Services (2000), assessment of current tobacco-use prevention and cessation activities is paramount in the development of a comprehensive strategy to reduce initiation, increase cessation, and reduce exposure to environmental tobacco smoke. Parallel to this recommendation, Bunnell et al. (2012) stated that future work to combat interrelated economic and health challenges could build on the Communities Putting Prevention to Work (CPPW) approach. Benefits from the strategic selection of priorities, robust support for individual community needs, and enhanced accountability to ensure fidelity to the design of program plans (Bunnell et al., 2012) may improve the CPPW approach in implementing evidence-based tobacco-use interventions.

Summary

In this chapter, I addressed smoking as the strongest avoidable risk factor for PC and CTSG-A along with other predictors (age, gender) emphasizing the intent of this study was not only to explore its likely modification effect among individuals with CPG but also to highlight the positive social change through smoking cessation. Moreover, the

call for further research on the procarcinogenic effects of smoking (Pandol et al., 2012) was acknowledged. Conceding the need to investigate the genetic and environmental interactions associated with the increased PC risk (Schenk et al., 2001) affirmed the significance of the development of prevention and control strategies and lifestyle changes to reduce cancer risk. Exploring predictors' association with CPG may contribute to the understanding of pancreatic carcinogenesis, critical to the advancement of efficient clinical practice.

The outcome of this study may provide valuable information to future researchers improving current understanding of genomic instability, one of the leading causes of genetic heterogeneity (Burrell et al., 2013). Previous studies indicated that this disease has a complex genomic landscape (Campbell et al., 2010). It was therefore critical to explore the extent of the current understanding of PC, to recognize the probable effect modification of smoking, and to examine the correlation of gender and age to disease initiation and progression among individuals with CPG. Chapter 2 provides an in-depth review of the literature addressing the cancer genome landscape, patterns, dynamics of genomic instability in PC evolution, and the etiopathogenic role of tobacco use. The accumulation of mutations in a variety of genes is discussed, antecedent to the procarcinogenic effects of smoking, making the disease a highly malignant tumor with few viable therapeutic options (Makohon-Moore et al., 2013).

Chapter 2: Literature Review

The early symptoms of pancreatic cancer (PC) often mimic other benign

conditions, and its biological complexity adds challenge to early detection, resulting in a

highly malignant tumor with few viable treatment options. The evolution of PC

progression involves its genetics from initiation to the tumor's ability to adapt and grow

even with intense therapy. The primary reasons for its poor clinical resistance are early

metastasis, chemoresistance, and late clinical outcomes. Asymptomatic in the early

stages, PC is a highly lethal cancer difficult to detect with a median survival of less than

6 months, and a 5-year survival rate of less than 5% (Klein, 2012). According to Yachida

et al. (2010), it takes at least 15 years from the time of the initiating mutation to

metastasis, making the tumor unresectable and aggressive in a metastatic state by the time

PC is diagnosed. Vital to the development of therapies, mapping of the PC genome that

target many genetic abnormalities will aid in the understanding of pancreatic

carcinogenesis, crucial in improving clinical outcomes.

The mechanisms through which smoking, gender, age, and cancer predisposition

genes (CPG) affect PC remain unknown, making it critical to explore the role of these

three predictors in the disease clustering to develop a more efficient management and

clinical approach. With an exhaustive understanding of the patterns of somatic alteration

in pancreatic carcinogenesis comes the opportunity to understand the influence of these

factors on metastatic progression (Yachida & Iacobuzio-Donahue, 2013). Working

toward this goal, the key intent of this dissertation was to highlight the pathopoiesis

mechanism of tobacco use and CPG, as well as the etiopathogenic role of gender and age. New research directions are warranted to reverse the lethal outcome of this disease.

In this chapter, I provide a scholarly review of literature related to the current state of understanding of PC. I searched for peer-reviewed studies on PC using the Thoreau database with a restriction on the year of publication from 2011 to 2016. Scholarly literature published before 2011 was considered to establish a historical perspective on the progression of pancreatic carcinogenesis research. Bookends On Tap, a reference management iPAD app, provided current articles across databases including PubMed, PubMed Central, Google Philomath, JSTOR, and arXiv. Using Evernote and Microsoft OneDrive, I conducted an automated search weekly to identify current literature using the myNCBI feature of PubMed. Blogs, non-peer-reviewed papers, and forum posts were omitted to ensure that references were of high quality.

Background

In the United States, smoking-related illness costs more than $300 billion each year (Warren, Alberg, Kraft, & Cummings, 2014), and since the 1970s tobacco use remains a major risk factor of PC. According to Pandol et al. (2012), accumulating evidence has indicated that carcinogenic compounds from tobacco use stimulate pancreatic cancer progression. Pandol et al. noted the economic burden of PC with an expected yearly cost of $4.9 billion and underscored the significance of determining the mechanisms underlying the effect of smoking compounds that may provide additional insights into the pathogenesis of the disease. The investigation gave valuable insights into the etiopathogenesis of pancreatic growth from its induction and promotion.

The present understanding and the surge of awareness of PC in the 21st century began with the significant progress achieved by the discovery of the human pancreatic duct in 1642 by Wirsüng, followed by Blobel's discovery of signaling mechanisms that govern the transport and localization of proteins within pancreatic acinar cells in 1999 (Ceranowicz, Cieszkowski, Warzecha, Kuśnierz-Cabala, & Dembiński, 2015). At present, solid tumors are interpreted as alterations in driver genes (Armitage & Doll, 1954; Vogelstein et al., 2013) that ordinarily require five to eight hits in classic epidemiologic studies. According to Vogelstein et al. (2013), several tumors have only one or two driver gene mutations, as shown in Figure 2. Given that cancer genome sequencing is a relatively new endeavor, the identification of three oncogene mutations and six alterations with both oncogene and tumor suppressor gene mutations in PC will give way to the most appropriate management plan (Vogelstein et al., 2013).

The outcome of cancer genome sequencing already had an impact on the clinical care of cancer patients. However, a greater emphasis on probabilistic thinking and clinician numeracy are essential in the development of new models for creating an efficient medical care system centered on the quality of care, extending and improving the quality of life for patients diagnosed with PC and CTSG-A. There is a need to integrate epigenetics, proteomics, and metabolomics in the analysis of genomic data, and the addition of a sophisticated clinical workforce (Krier & Green, 2013) will contribute to the management of incidental findings. Additionally, given the significant environmental factors' role in the etiology of sporadic pancreatic cancer (Raimondi, Maisonneuve, & Lowenfels, 2009), it is necessary to develop diagnostic tests that not only aid in the

identification of susceptible individuals or monitor disease progression, but also aid in
prevention or guide PC treatment (Hocevar et al. 2014).
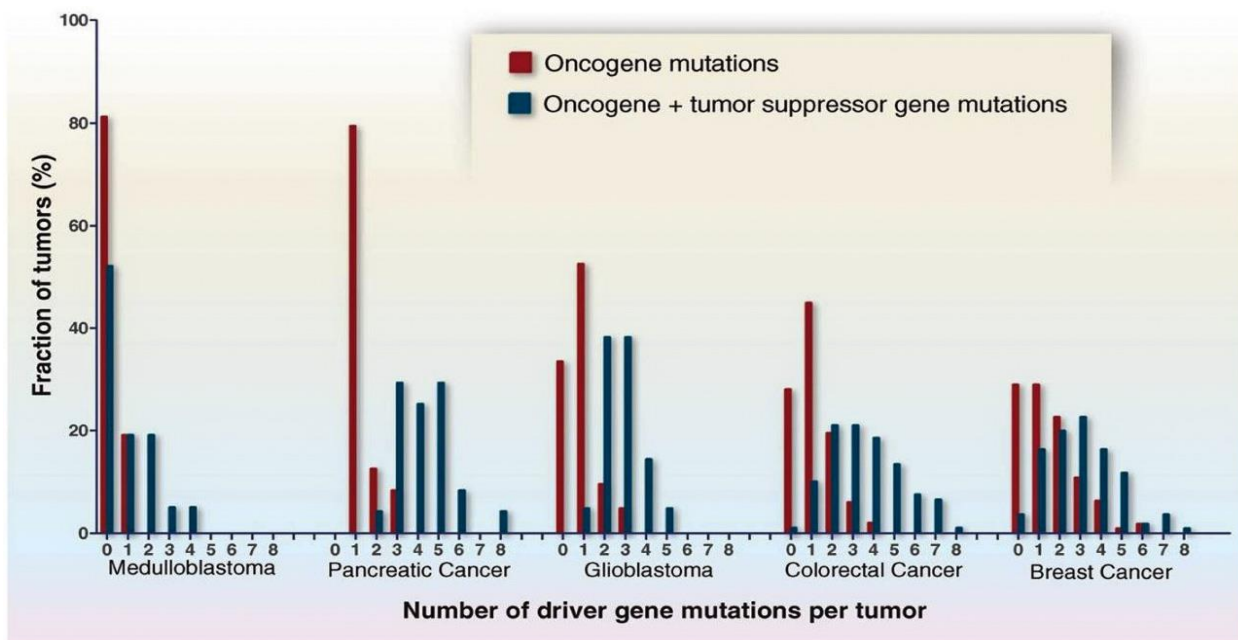
Figure 2. The number and distribution of driver gene mutations in pancreatic cancer
compared to other tumor types (Vogelstein et al., 2013, p. 29).

Pancreatic Cancer Genetic Landscape and Molecular Biology

Subject to evolutionary paradigms, PC emerged as a disease of inherited and
somatic mutations from more than two decades of research (Maitra & Hruban, 2008).
Sequencing of the germline of individuals with a strong family history of pancreatic
cancer and those with a genetic predisposition to the disease is critical to raising
awareness of the promise of extrapancreatic neoplasm screening in identifying early
curable pancreatic neoplasia (Iacobuzio-Donahue, Velculescu, Wolfgang, & Hruban,
2012). There are three important points to remember about the germline genetic
syndromes (GGSs) associated with lifetime PC risk. First, quantifying PC risk of known

genes responsible for the aggregation of PC in a family is necessary for the design of clinical trials of at-risk patients screening for early curable precancerous lesions (Canto et al., 2012; Canto et al., 2013). Second, both high and low-penetrance genes except genes associated with familial pancreatitis increase the PC risk and extrapancreatic malignancies. Lastly, although screening for extrapancreatic malignancies can save lives, it is important to remember that some of these GGSs have implications for therapy. The changes in the clinical management of neoplasms with somatic mutations begotten by the sequencing of the most common types of pancreatic tumors warrant the search for new strategies in the early detection and treatment of pancreatic neoplasia (Wolfgang et al., 2013).

Endocrine and exocrine pancreatic tumor genetics and biology can be profoundly influenced by the particular type of origin, exhibiting considerable divergence in their mutational spectra and clinical behavior (Jiao et al., 2011). With regard to the evidence for clonal diversity between primary and metastatic sites, Campbell et al. (2010) found the amplification of cancer genes predominantly occurring in early cancer development and genetic heterogeneity among metastasis-initiating cells. The data presented in this study confirmed the richness of genetic variation in cancer. Like Campbell et al. (2010), Waddell et al. (2015) also discussed the genomic instability concerning cancer dissemination and metastases. In addition to numerous genes mutation at low prevalence, Waddell et al. substantiated the importance of V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), Tumor protein p53 (TP53), SMAD Family Member 4 (SMAD4), cyclin-dependent kinase Inhibitor 2A (CDKN2A), and AT-Rich Interaction

Domain 1A (ARID1A) gene mutations. Waddell et al. found the role of chromatin modification and the broader role for aberrant Wnt signaling pathway (KW-0879) in recurrent mutations identified in Lysine Demethylase 6A (KDM6A). Waddell et al. provided the most comprehensive description of the genomic events that characterized pancreatic cancer and demonstrated the prominent structural variation mechanism of genomic damage in this disease.

Worldwide, 85% of PC cases are adenocarcinomas, and 1 to 10 cases per 100,000 have the incidence of all types of PC. According to Ryan, Hong, and Bardeesy (2014), PC has ranked as the eighth leading cause of death among men, and the ninth leading cause of death among women globally for the past 30 years. Like Blackford et al. (2009), Ryan et al. found the role of KRAS mutations in the etiopathogenesis of the disease. Given the risk factors and established genetic syndromes associated with the condition (see Table 1), and despite the unidentified genetic basis of familial aggregation, Ryan et al. agreed with Klein et al. (2004) that PC has the estimated 5 to 10% unidentified inherited component in familial aggregation. Somatic structural rearrangement of chromosomes as part of the mutational landscape of PC could lead to the development of novel screening, surveillance, and therapeutic strategies.

Table 1

Risk Factors and Inherited Syndromes Associated With Pancreatic Cancer

Variable	Approximate risk
Risk factor	
Smoking (Bosetti et al., 2012)	2-3
Long-standing diabetes mellitus (Ben et al., 2011)	2
Nonhereditary and chronic pancreatitis (Duell et al., 2012)	2-6
Obesity, inactivity, or both (Aune et al., 2011)	2
Non–O blood group (Klein et al., 2013)	1-2
Genetic syndrome and associated gene or genes— %	
Hereditary pancreatitis—PRSS1, SPINK1 (Rebours et al., 2008)	50
Familial atypical multiple mole and melanoma syndrome—p16 (Vasen et al., 2000)	10-20
Hereditary breast and ovarian cancer syndromes—BRCA1, BRCA2, PALB2 (Iqbal et al., 2012; Jones et al., 2009)	1-2
Peutz–Jeghers syndrome—STK11 [LKB1] (Giardiello et al., 2000)	30-40
Hereditary nonpolyposis colon cancer (Lynch syndrome)—MLH1, MSH2, MSH6 (Kastrinos et al., 2009)	4
Ataxia–telangiectasia—ATM (Swift et al., 1991)	UNKN
Li–Fraumeni syndrome—P53 (Ruijs et al., 2010)	UNKN

Note. Adapted from "Pancreatic Adenocarcinoma" by D.P. Ryan, T.S. Hong, and N. Bardeesy, 2014, *New England Journal of Medicine,* 371(11), p.1040. Copyright 2014 Massachusetts Medical Society. UNKN = Unknown.

To date, surgical resection remains the only potentially curative treatment according to Zakharova et al. (2012), albeit only 15%-20% of patients with PC are good candidates for the procedure. On the other hand, the focus of health care providers on prolonging life, helping patients and their family through difficult transitions after diagnosis are equally as important as improving survival through the development of optimal treatment algorithm (Wolfgang et al.,2013). The increased use of high-quality multi-detector computed tomography (MDCT), neoadjuvant treatment with systemic chemotherapy, and the enormous strides in exploring the underlying genetics of pancreatic cancer are critical parts of an individualized treatment algorithm (Varadhachary et al., 2006; Zakharova et al., 2012). The outcome of this dissertation in combination with such an innovative, evidence-based treatment plan could improve perioperative care and quality of life.

The particular application of past and current research on inherited mutations to this dissertation supports an earlier study by Tersmette et al. (2001) that demonstrated the risk of developing PC among first-degree relatives (FDRs) in the family with the disease. In this study, the researchers found that PC kindreds with three or more affected relatives show a 57-fold (95% CI = 12.4–175) increased the risk of pancreatic cancer. Tersmette et al. (2001) stated that although the gene or genes responsible for familial PC have not yet been identified, the findings highlighted the importance of the development new PC chemoprevention and screening modalities that will benefit this group of individuals (p. 733). Following this point of inquiry, Ludwig et al. (2011) delve into the rationale for strategies in identifying early detection of precursor lesions or early cancers in high-risk

groups that could improve disease-specific outcome. The researchers perused the significant yield of screening at-risk relatives of familial pancreatic cancer patients. Magnetic resonance cholangiopancreatogram (MRCP) was used to screen 309 asymptomatic at-risk relatives enrolled in the Familial Pancreatic Tumor Registry (FPTR) of Memorial-Sloan Kettering Cancer Center (MSKCC) to validate the results of prior studies as to the safety and efficiency of MRCP as an initial screening modality. If indicated, endoscopic ultrasound with fine needle aspiration was performed. MRCP produced a significant diagnostic yield, particularly in family members >65 years of age.

Akin to the objective of the study of Ludwig et al. (2011), an earlier investigation by Klein et al. (2004) examined the significance of familial PC history (FPCH) as a rational basis for cancer risk screening and counseling. In this prospective registry-based study, using the National Familial Pancreas Tumor Registry (NFPTR) as a resource of familial pancreatic cancer (FPC), Klein et al. contrived the probable denotative increased risk of pancreatic cancer in FPC kindreds. The quantification of family members diagnosed with the disease supported the hypothesis of increased risk among individuals with FCH. The study found an increased PC risk with burgeoning numbers incidence among FDRs. Parallel to this rationale, several studies asserted a two to a five-fold excess of pancreatic cancer in FDRs of patients with PC, augmented among smoking relatives of patients with the disease (Brentnall et al., 1999; Schenk et al., 2001). The prospective, registry-based study of Klein et al. (2004) help quantified the risk of pancreatic cancer in kindreds in which a family member has received a diagnosis of PC (p.2637). The findings added to the body of evidence that the familial aggregation of pancreatic cancer is often

not due to chance, and demonstrated that a strong family history of PC significantly increases the risk of PC development.

Complex Darwinian Evolutionary System

Parallel to the Darwinian natural selection, Peter Nowell's landmark perspective on cancer as an evolutionary process is driven by stepwise, somatic cell mutations with sequential, subclonal selection (Nowell, 1976). Considered as a legitimate scientific theory, the evolutionary theory of cancer has survived 35 years of empirical observation and testing (Greaves & Maley, 2012). Whereas the understanding of the essential components of somatic evolution is well established, Greaves and Maley (2012) noted the tools from evolutionary biology that may be applied to neoplasms to give light on the uncertain disposition on the dynamics of somatic evolution and address the fundamental questions in cancer biology. The diverse mutational processes involved in carcinogenesis, modern cancer biology, and genomics validated cancer as a complex, Darwinian, adaptive system (Merlo et al., 2006; Greaves & Maley, 2012). Using a non-spatial population genetics model of sequential, exponential clonal expansion, Bozic et al. (2010) formulated an equation to pancreatic cancer resequencing data in estimating driver mutation. The empirical evidence established by tumor biology and genetics on the considerable divergence in the mutational spectra and clinical behavior of endocrine and exocrine PCs emphasized the need to advance genomics technologies (Jiao et al., 2011). Furthermore, Jiao et al. (2011) noted that making improvements on genomics technologies will heighten the understanding of how genomic instability shapes tumor evolution. While genomic instability may be an attractive therapeutic target; such

weakness can leave distinct genomic footprints through various routes, affecting tumor development and patient outcomes (Burrell et al., 2013).

The genetic complexity of PC, hampers the progress in the identification of novel therapies, making the early diagnosis of the disease as one of the few options for improved outcomes (Hidalgo et. al, 2015). Such complexity made the dynamics of clonal diversification and selection in the foreground to understand neoplastic progression and response to therapy. According to Greaves and Maley (2012), the control, delay or prevention of cancer mortality is dependent upon the clinical opportunities to address evolutionary adaptability of neoplasms. Applying the evolutionary clock model to the number of mutations that have been quantified in tumors representing progressive stages of PCs lead to two definite conclusions (Jones et al., 2008; Yachida et al., 2010; Vogelstein et al., 2013). First, a full-blown, metastatic cancer takes decades to develop, and mutations are already virtually present in a significant number of cells in the primary tumors (Vogelstein et al., 2013). Second, the timing of mutations verbalized in this study is relevant to our understanding of metastasis (Vogelstein et al., 2013), fortifying the desideratum for the development of new screening modalities that will justify preventive surgical intervention.

The new insights into the biology and genetics of PC, recognizing CDKN2A (G1 cell cycle arrest pathway) and p53 (p53 pathway) argued by Ryan et al. (2014) as the commonly mutated oncogenes in this study, in addition to new findings regarding KRAS mutations, tumor metabolism, and tumor immunology, may be of value in the development of new treatments. In addition to discoveries regarding KRAS mutations,

tumor metabolism, and tumor immunology, Ryan et al. (2014) emphasized the importance of new insights into the biology and genetics of pancreatic cancer, essential elements in the development of new treatments. Given the paucity of documented presence of branched evolution and clonal diversity between primary and metastatic sites in pancreatic tumor development (Campbell et al., 2010; Yachida et al., 2010), cancer genomes can be exploited for elaborating the need for developing more effective immunotherapies (Vogelstein et al., 2013).

The Whole-genome and Whole-exome data analyzed in the 2013 study of Lawrence et al. suggest a strong correlation between somatic mutation frequency in cancers and gene expression level. Lawrence et al. (2013) focused on two dominant factors that explain mutational heterogeneity: the gene expression level where the germline mutation rate affected by transcription-coupled repair, and replication time of a DNA (deoxyribonucleic acid) region during the cell cycle (Fousteri et al., 2008; Pleasance et al., 2010). Based on the analysis of the massive amounts of whole-genome sequencing, Lawrence et al. (2013) concluded that the accurate accounting of mutational processes is dependent upon the precise identification of new cancer genes. Relevant to the discussion of mutational processes, it would be beneficial to note the association of the familial clustering of PC with several features of the genetic syndromes. Individuals with a strong family history of PC with a first-degree relative with the disease have a 2.3-fold increased risk of developing the malignancy (Amundadottir et al., 2004). The increased risk that could be explained by an autosomal dominant inheritance of a rare allele (Klein et al., 2004); Maitra and Hruban (2008) noted that the association of the

disease with some germ-line genetic alterations could provide insights into its

pathogenesis. While the absence of a strong family history of cancer cannot be used to

rule out a germline mutation, according to Maitra and Hruban (2008) shown in Table 2—

most of the germline mutations except those in the Protease, Serine 1 (PRSS1) gene are

associated with an increased risk of extrapancreatic malignancies.

Table 2

Germline Mutation Genes

Individual	Gene	Relative risk	Risk by age 70	Cancer morphology	Other cancers	Reference(s)
No history	None	1	0.5%	NS	None	
Breast Cancer	BRCA2	3.5-10x	5%	NS	Breast, Ovary, Prostate	Goggins et al., 1996; Ozçelik et al., 1997
	BRCA1	2x	1%	Breast cancer with basaloid features		Lynch et al., 2005
FAMMM	P16 (CDKN2A)	20-34x	10%-17%	NS	Melanoma	Bartsch et al., 2002; Parker et al., 2003
Familial pancreatic cancer (3 FDR)	UNKN	32x	16%	NS	UNKN	Klein et al., 2004
Familial pancreatitis	PRSS1	50-80x	25%-40%	Pancreatic cancers in the background of severe diffuse chronic pancreatitis	None	Lowenfels et al., 1997
Peutz-Jeghers	STK11/LKB1	132x	30%-60%	NS	Gastroesophageal, small bowel, colorectal, breast	Su et al., 1999; Giardiello et al., 2000
HNPCC	bMLH1, bMSH2, others	UNKN	< 5%	Medullary and colloid phenotypes	Colorectal, endometrial, stomach, ovarian, ureter and renal, pelvis, biliary tract, brain	Goggins et al., 1998; Yamamoto et al., 2001
Young-age-onset pancreatic cancer	FANC-C and FANC-G	UNKN	UNKN	NS	UNKN	Van der Heijden et al., 2003; Couch et al., 2005

Note: Genes associated with an increased risk of pancreatic cancer: 3 FDR, 3 or more first-degree relatives with PC; FAMMM, familial atypical multiple mole melanoma syndrome; HNPCC, hereditary non-polyposis colorectal cancer syndrome; NS, non-specific. UNKN = Unknown.

From an Evolutionary Model to the Unified Paradigm of Cancer Causation (UPCC)

Three important events launched the field of cancer epidemiology during the 18th century. First, is Bernardino Ramazzini's study on cervical cancer in 1713, the research of Percival Pott in 1775 that led the way on occupational carcinogenic exposure studies, and Thomas Venner on the danger of tobacco use in his Via Recta, published in London in 1620 (American Cancer Society, 2014). After two centuries when John Hill wrote a book entitled "Cautions Against the Immoderate Use of Snuff" in 1761; Krain (1970), along with other studies in the 1970s, Wynder, Mabuchi, Maruchi and Fortner (1973) explored the causality of tobacco use in the development of PC. Jones et al. (2008) found that PCs have an average of 63 genetic alterations that can explain the major features of pancreatic tumorigenesis. The intensive genetic studies described by Jones et al. (2008) gave way to the better understanding of the core set of pathways and processes, embracing the idea of Owens, Coffey, and Baylin (1982) that tumor heterogeneity is a fundamental facet of all solid tumors. While PC has few viable treatment options, Jones et al. (2008) suggested that the best hope for therapeutic development may lie in the discovery of agents that target the physiologic effects of the altered pathways and processes rather than their gene components. Above all, the significance that could not have been appreciated in the absence of global analysis is the identification of the precise

genetic alterations that may be responsible for tumor pathway dysregulation (Jones et al., 2008).

The pathogenic theory of medicine or the germ theory of disease was highly controversial when first proposed as a concept that microorganisms are the cause of many diseases. After validation in the 19th century, germ theory revolutionized both medical thought and the art of surgery, becoming a fundamental part of modern medicine and clinical microbiology. The UPCC, a metatheory in this dissertation as a composite of germ theory and Darwinian evolutionary system (Greaves & Maley, 2012) along with other theories mentioned in the previous chapter will provide clarity on the narrative of the initiation of PC. Albeit the acceptance of the somatic mutation theory of carcinogenesis (SMT) as the mainstream narrative of how neoplasms develop (Soto & Sonnenschein, 2004), SMT included in the UPCC's cocktail of theories will build on the arguments of the core principle of genetic variation and pattern of mutations (environmental and genetics) that are sufficient probable causes of the disease. In this chapter, UPCC will explain the behavior of PC cell in rationalizing the complex array of the possible interaction of smoking and inherited genes.

Pancreatic cancer is the fourth commonest cause of cancer death in Western societies and is projected to be the second leading cause within a decade (Waddell et al., 2015). As a consequence, this dissertation will address the urgent need to follow through in the assessment of EGBIs and fill the gap of prior studies of not considering the reasonable modification of environmental exposures (smoking) to the genomic landscape of the disease. While using the Darwinian methods links human sociocultural progress to

genetic evolution (Richerson & Boyd, 2000); Lynch and Rebbeck (2013) used a "Multi-level Biologic and Social Integrative Construct" (MBASIC) to integrate macro environment and individual factors with biology. Considering the limitation and information generated by single-level studies have reached a saturation point (Lynch & Rebbeck, 2013), this dissertation acknowledges the significance of individual level (behaviors, carcinogenic exposures); and biologic level (inherited susceptibility variants). Germline changes associated with PC (see Appendix) could range from slightly increased risk (low penetrance genes) to high lifetime risk (high penetrance genes). Given that PC is the antecedent of inherited (germline), and acquired (somatic) mutations in cancer-causing genes, adding the probable correlation between gender and age, modifying effect of smoking to the equation that could trigger or wake up a sleeping germline mutation could position the result of this dissertation for improved public health intervention, translation and implementation in clinical settings to alter the expression of the disease.

Smoking: A Modifiable Behavioral Risk Factor

Tobacco smoking is recognized as a significant environmental factor and the strongest avoidable risk factor, and Pandol et al. (2012) highlighted the need for further research on its procarcinogenic effects. The gap of this 2012 study was explored by Schulte et al. (2014), and the researchers comprehensively discussed the tobacco component primarily relevant to pancreatic cancer risk (PCR). Regression models were employed in this study generating statistical results broadly consistent with the association of both smoking intensity and smoking duration to PCR. The conclusion justified the role of smoking pattern in the greater risk of developing the disease. While

Pandol et al. (2012) and Schulte et al. (2014) are closely akin in investigating the association between cigarette smoking and PC, the outcome of the study of Schulte et al. (2014) complements the findings of Blackford et al. (2009) on DNA damage as the antecedent of tobacco carcinogens. Whereas the study confirmed an increased mutation trends among smokers, in contrast to previous research, the researchers did not observe an association between KRAS gene mutations and tobacco use. KRAS is one of the molecular switches in signal transduction and one of the genes belonging to the Ras gene family. Malignant Phenotype cell transformation is the direct result altered by protein products expression generated by point mutations in codons 12, 13, and 61 of KRAS (Vogelstein et al., 2013).

Blackford et al. (2009) demonstrated the best use of methodology and statistical approach that helped explore the number of mutations in PC in association with cigarette smoking. Given that smokers may develop the disease more frequently at a younger age, the researchers found no difference between the mutation of driver genes among smokers and non-smokers. The types and patterns of mutations found in PC, provided insight into the mechanisms by which cigarette smoking causes the disease (Blackford et al., 2009). While the mutations found on PC, have a strong association with cigarette smoking, the findings in this study did not produce a characteristic profile. Like Crous-Bou et al. (2007), Blackford et al. (2009) noted that previous researchers overlooked the distinction between the passenger and driver mutations that explains the often unconvincing associations between smoking and driver mutations. Recognizing this gap, and while there are continued studies on different aspects of the PC genomic landscape, the intent

of this dissertation is to provide a descriptive analysis of the prevalence pattern of PC and CTSG-A known to have increased risk of extrapancreatic malignancies versus non-smokers.

Connecting the Dots: Smoking and Genetic Aspects of Pancreatic Cancer

The lack of effective screening tests makes the detection and treatment of PC an Augean task, albeit the substantial gains in the last 40 years on the knowledge of its epidemiology. The past efforts into understanding the pathosis and epidemiology of PC established the basis for scholarly introspection on many current inquiries focused on the association of modifiable risk factors and inherited mutations. The goal of the past and present studies falls largely within the confines of understanding the insights of genetic alterations and specific modifiable risk factors. Much of the recent research concentrates in this line of inquiry; therefore, recognizing the modifying effect of smoking to individuals with family aggregation justifies the merit of this dissertation and future endeavors.

Parallel to the study of Klein et al. (2004), Wolfgang et al. (2013) found the significant role of tobacco use in the etiopathogenesis of PC to higher smoking rate among first-degree family relatives (FDRs) of individuals diagnosed with the disease. The findings in these studies suggest that smoking cessation may be particularly useful in the familial PC kindreds. Kumar et al. (2014) also examined the pathopoiesis mechanism of tobacco use in early stage PC using genetically engineered mouse model (LSL-K-rasG12D). The study found accelerated formation of pancreatic intraepithelial neoplasia (PanIN) lesions in response to smoking and the switching of markers from acinar to

ductal type, suggestive to enhanced acinar-to-ductal metaplasia (ADM). In this study, the

experimental epidemiological data provided a novel mechanism of smoking that induced

ADM in the presence of constitutively active KRAS mutation. The findings of Kumar et

al. (2014) enhanced the existing body of knowledge on the role of smoking in the

etiopathogenesis of PC and opened the gap on the need to explore its modification effect

among individuals with CPG.

Hart, Kennedy, and Harvey (2008) asserted the need for further epidemiologic

work in clarifying the association of PC with many exposures using a precise

measurement of risk factors, and adjustment of potential confounders. Schenk et al.

(2001) conducted routine questioning of patients on the family history of PC, the age of

onset of the disease among relatives, and patient's smoking status. The study assessed the

higher risk of PC in FDRs, and the effect of smoking on disease onset among younger

individuals. Schenk et al. (2001) found that while family history of PC, the age of onset

of the disease among relatives and patient's smoking status may identify individuals at

high risk, it is vital to explore the genetic and environmental interactions (GEIs)

associated with the disease in future research. The only way to move forward in any

research endeavor is to revisit the outcomes of past and ongoing studies. From this

overview, it is clear that numerous research on the role of smoking and CPG in the

etiopathogenesis of PC has contributed to the understanding of the epidemiology of the

disease. The findings of these studies support the unique probable contribution of this

dissertation to the existing body of knowledge, generating a snapshot of a possible

correlation of smoking, gender, and age to the development of PC and CTSG-A,

enhancing the knowledge on the pathopoiesis mechanism of these predictors in disease induction and promotion. The plethora of findings of the past and present studies highlighted the causal significance of modifiable risk factors and genetics in the pathosis of PC. It would be worthy to discuss further in this chapter its epidemiology, and the genetic basis of its development and progression.

Bridging Cancer Epidemiology and Social Evolution

Modern epidemiology is a direct result of the paradigm shift from a population-based (upstream) to a downstream (individual) approach. The impact of modern epidemiology such as 'molecular' and 'genetic' epidemiology (Loomis & Wing, 1990; Diez-Roux, 1998) requires an explanatory power that largely dependent upon the advances in technology and information systems. The development of the new epidemiologic shift recognizes not only the significance of sophisticated technologies that go beyond the established genome, proteome, and gene expression platforms, but also new techniques of study design and data analysis (Pearce, 1996; Verma, Khoury & Ioannidis, 2013). Given the remarkable progress in the last decade in advanced technology and new methods for biologic measurements, the reductionist approach of modern epidemiology often ignored the major causes of disease. Pearce (1996) argue that epidemiology must reintegrate itself into public health and must rediscover the population perspective. However, while the new paradigm could produce a lifestyle approach to social policy, the cumulative outcome of research in cancer epidemiology could equate positive implications to population health.

The key figures in the new epidemiologic model not only acknowledges the development of new techniques of study design and data analysis but also recognize the need for a multidisciplinary approach (social, biologic, statistical), and specifying the population group as the unit of study (Susser, 1985). While occupational carcinogens can be controlled with some difficulty through regulatory measures (Pearce, 1996), it is important to acknowledge the fundamental problem of tobacco use is not by its consumption but lies in its production. Pearch (1996) focused on some of these fundamental changes in epidemiology over the past few decades and considered the concepts of causality involved, as well as their ideological and practical consequences. While smoking cessation is the probable social implication of this dissertation, it is important to stress the epidemiologic value of a study on the apparent correlation between gender and age, modification effect of tobacco use among individuals with PC and CTSG-A. The outcome of a risk factor epidemiologic study in individual terms could uplift precision medicine to meet the challenges in tailoring medical interventions based on patient's biological profile, genetic and epigenetic traits, giving a better understanding of EGBIs.

Embraced by both biomedical and social determinist frameworks, the interlinking of the traditional epidemiologic level of intervention (upstream or distal) and the modern epidemiologic level of intervention (downstream or proximal) put public health in the conundrum of the proximal-distal divide. Signal the importance of the argument of the 2008 study of Krieger in replacing the terms proximal and distal from the public health lexicon, supports the recommendation of Wemrell et al. (2016) on the critical need for

open interdisciplinary debates on the contribution of social theory to the epidemiological

inquiry. While coping with the demand of the 21st-century, global health could still be

viewed and approached within the mindset of traditional epidemiology, and the purview

of molecular and cancer epidemiology.

The discovery of tobacco smoking as a cause of lung cancer in the early 1950s

gave the field of epidemiology its recognition (Pearce, 1996), shifting the epidemiologic

paradigm in the object of study in the mid-20th century on the role of multiple causes.

Establishing the correlation of age, gender a modifiable risk factor (smoking) with PC

and CTSG-A requires the use of early and current epidemiologic theories, and

contemporary mainstream epidemiologic concept coalescing to a UPCC. The complex,

integrative approach of UPCC supports the views of Loomis, and Wing (1990), Pearce

(1996), and McEwen and Getz (2013) in embracing the new epidemiologic paradigm

congruent to the advances in cancer genome sequencing. Theorizing the pathopoiesis

mechanism of smoking, inherited genes, and association of gender and age in the

etiopathogenesis of PC/CTSG-A warrants exploration of its causal footprints, conjoining

both biomedical and lifestyle (Krieger, 2011).

In this dissertation, follow-up and future research are highlighted on the role of

molecular epidemiology in emphasizing individual susceptibility to PC will assess the

relative contribution of modifiable risk factors to non-modifiable genetic factors. In this

premise, the etiopathogenesis of the disease could be explored from the bottom up.

Bridging cancer epidemiology and social evolution will be dependent upon the

incorporation of the strength of the social network and social contagion theory. The

testable assumption of the social network theory as its strength states that the social structure of the network itself be primarily responsible for determining individual behavior and attitudes by shaping the flow of resources which determines access to opportunities and constraints on behavior (Berkman et al., 2000). Why choose if a single theory cannot make a change? Incorporating these ideas in addition to the composite and underpinnings of UPCC could springboard a priori argument on the role of social networks in the spread of an intervention such as smoking cessation, or amplifying the promotion of the significance of early screening to improve mortality and morbidity.

While the causal nature of peer effects could be associated with tobacco use; the social contagion theory of Christakis and Fowler (2013) set an argument on human social networks exhibiting a "three degrees of separation." Such association could support the assumption of spreading the interpersonal influence the acknowledgment of the significance of early screening, and the promise of a novel therapeutic approach. Like the widely discussed classic paper of Travers and Milgram (1969) on 'six degrees of separation,' the three degrees of separation or the three degrees of separation rule (Christakis & Fowler, 2009) agreed on the premise that telegraph phrases are meant to be evocative, and not definitive. For example, the role of interpersonal influence in spreading novel ideas such as advances in early screening to achieve a greater therapeutic outcome. The preponderance of the evidence that points to the added significance of a passive-broadcast viral messaging to create social contagion warrants the recognition of the approach. Taking into account factors such as the promise of the outcome of a research study in the quality of life, social and economic incentives could expand the

social network and amplify social support needed by individuals with PC or any deadly diseases. According to Kroenke et al. (2013), effective social support interventions need to evolve beyond social-emotional interventions and need to account for disease severity and treatment status.

Personal Genomics, Screening, Surveillance, and Management

Reducing the cancer-specific mortality of PC lies in early diagnosis and treatment (Lennon et al., 2014). Ideally, early detection of the disease should be at precancerous stage, and according to Lennon et al., (2014) there are six issues needed to be addressed. First is the characterization of the curable lesions, distinguishing the advanced from non-curable. Second, identify the reasonable window of opportunity to detect localized treatable lesions. Third, development of a test or screening tools that could determine the compendium of curable localized lesions. Fourth, a method to assess and distinguish localized lesions that are treatable from localized lesions that have a reasonable chance of progression. Fifth, development of novel screening tests or biomarkers with high positive predictive value. Lastly, the continued evidence-based research on the significance of early screening as well as research on the understanding of PC's biological processes that have potential implications for the understanding of its etiology, prevention, and therapy. Driven by the accumulation of somatic mutations, PC epigenetic modifications, and changes in the microenvironment warrant new strategy to investigate disruptions of gene expression networks that could uncover key regulators and pathways in carcinogenesis (Hoskins et al., 2014).

The utilization of population-level screening tests utilizing registered tomography (CT) despite neither indisputable confirmation nor proficient assertions about the adequacy and cost-viability has been promoted to patients through dissemination into practice on amid the previous decade (Burger and Kass, 2009). Inquiries regarding doctors' proficient roles and responsibilities within the setting of medical advancement shroud this phenomenon, including the appropriate scope of patient autonomy and access to unproven screening technology. Burger and Kass (2009) recognize the medical and ethical contrasts between screening recommendation for an individual patient and a population health premise. Particular cases were examined to investigate how risk factors, evidence, and inclinations impact singular patient screening choices. Direction on how screening ought to be done is obscured by specialists' attention on ethics, communication, and governmental issues. The proposal of Rychetnik et al. (2013) on expanded evidence-based cancer screening policy and practice could yield significant implications on cancer screening research. Stadler et al. (2012) analysis of the literature found the association of both BReast CAncer gene one (BRCA1) and BRCA2 mutations with the incidence of pancreatic cancer and BRCA2 mutation in the increased risk of developing PC. Lucas et al. (2014) proposed environmental and genetic factors as causes of PC with BRCA2 gene as the genetic factor of particular importance. The risk of pancreatic cancer increases in the individual who has a close relative with the disease, with approximately 5-10 % believed to show familial clustering (Lynch et al., 2004; Cavanagh & Rogers, 2015). According to Naderi and Couch (2002), PC and germline BRCA2 mutations have a younger than average age of onset and tend to be of Ashkenazi

Jewish descent. Cavanagh and Rogers (2015) stated that cancer cases among individuals with CPG might be due in part to environmental factors or other genetic factors rather than possessing a BRCA1/2 gene mutation. Parallel to this argument, this dissertation hopes to inquire about the presumable alteration impact of smoking as a biological and modifiable hazard in the PC/CTSG-A induction and promotion.

Epidemiological theory as argued by Krieger (2011) is the practical necessity of thinking about and explaining disease distribution. The combined views of Fernandez, La Vecchia and Decarli (1996), Lynch et al. (2009), and Maisonneuve and Lowenfels (2010) postulates that the key measures to reduce PC are primary prevention in the form of tobacco smoking control or smoking cessation. In this context, given the cornucopia of knowledge proliferation from germ theory at its inception to the emerging scientific theories on cancer dynamics initiated by the classical evolutionary principles of the Darwinian theory (Barbara et al., 2014) forms an integrative web of theoretical causations that supports the proposed metatheory in this dissertation referred to as UPCC. Evolutionary models and theories vary substantially between gene and culture (Claidière & André, 2012). Richerson and Boyd (2000) added to this debate the methodological approach of the Darwinian theory. Darwinism is a collection of concepts, empirical methods and mathematical tools designed to understand the dynamics of genetics and cultural evolution (Richerson & Boyd, 2000). Therefore, this dissertation supports the rationale of cultural value transmission of smoking cessation that could lower the risk to individuals with CPG. Smoking cessation as a cultural item is a clear implication for positive social change.

The dynamic interplay of gene-culture transmission recognized in UPCC could initiate the evolution of culture that embraces the value of evidence-based screening, surveillance, management, and personal genomics. Central to human adaptations is the use of socially learned information (Richerson, Boyd & Henrich, 2010), from literacy program of a health system, emphasizing the significance of 21st-century approach. The combined causal association of a variety of levels as recognized by Lynch and Rebbeck (2013) that are linked to cancer incidence and mortality justify the supposition of UPCC. It is critical to underscore the magnitude of intercalating the mandatory early screening, and management of the health system. Moreover, it is also vital to showcase the weight of the cumulative evolution of complex adaptations on the invaluableness of genomics to gene-culture coevolution. Acknowledging the health system as a macroenvironment factor, in addition to social determinants and environmental exposures such as smoking will improve intervention, translation, and implementation.

While the 2013 study of Lynch and Rebbeck presented the MBASIC to integrate macroenvironment and individual factors with biology; UPCC as an integrated framework acknowledge the significance of embracing personal genomics, evidence-based surveillance, screening, and management rooted in a culturally transmitted macroenvironment. Should we be tampering with the human genome? The ethical, social, and clinical implications of personal genomics continue to trigger debate among research communities. Such discussions are a much-needed equipoise to the value of personal genomics for understanding disease pathogenesis, vital to improving the prognosis of a deadly disease like PC (McGuire et al., 2007; Zakharova et al., 2012; Nagpal et al.,

2014). Parallel to this view, Canto et al. (2013) purport the merit of surveillance, screening, and management of high-risk individuals (HRI) with an inherited predisposition to PC, establishing a consensus that high-risk individuals warrant pancreatic screening. An earlier study of Canto et al. (2012) asserted the need for continued research for optimal method of screening people with an inherited increased risk for PC. In this study, the researchers conveyed that rather than focusing screening efforts to detect invasive cancers, PC screening, and surveillance program should be in identifying and selectively treating asymptomatic high-grade precursor neoplasms. Debates over these issues, Zakharova et al. (2012) further argue the need for evidence-based consensus on the optimal preoperative imaging assessment of patients with suspected PC and a unified definition of borderline resectable tumors. Given that multi-detector computed tomography has been widely accepted, it is necessary to embrace a realistic approach concerning the patient's age, health status, quality of life and recovery after surgery. The practical approach discussed in this study on screening, surveillance, and management, as well as the improvement in the early detection and prevention, is dependent upon the progress in the understanding of the genetic alterations in PC and associated precursors and development of biomarkers.

New Public Health Meets a New Initiative on Precision Medicine

There has been a rapid expansion of knowledge about human DNA structural and sequence variation, since the completion of the Human Genome Project (HGP) in 2001 (Hood & Rowen, 2013). The growth of publicly available data sets and literature mining databases inspired by the HGP's open approach to data sharing gave way to the

identification of commonly dysregulated gene expression networks in pancreatic ductal

adenocarcinoma (PDAC) that could provide insight into the mechanisms of tumor

progression (Califano et al., 2012). PDAC is the most common sporadic pancreatic

cancer, driven by the accumulation of epigenetic modifications, somatic mutations and

changes in the micro-environment (Hoskins et al., 2014). A genome-wide approach was

used by Hoskins et al. (2014) to profile gene expression changes between normal derived

pancreatic samples and tumor. The data examined in this study in the context of

expression gene sub-networks, implicated a novel, central role for hepatocyte nuclear

factor 1 alpha (HNF1A) and corroborated the benefits of HNF1A down-regulation in the

proliferation and survival of pancreatic tumor cells. HNF1A is a transcription factor that

is known to maintain homeostasis of the endocrine pancreas that regulates pancreatic

differentiation (Luo et al., 2015). Evident in murine Sleeping Beauty transposon-

mediated somatic mutagenesis models of pancreatic cancer, Biankin et al. (2012)

identified various and diverse somatic aberrations in genes described traditionally as

embryonic regulators of axon guidance, particularly slit glycoprotein (Slit) and

Roundabout receptor (Robo) signaling. The study provided further supportive evidence

for the potential involvement of axon guidance genes in pancreatic carcinogenesis (p. 3).

The burden of chronic diseases such as PC is often neglected on the public

agendas. The increasing annual economic burden of PC is beyond genetics and social

inequalities, making it necessary to embrace the shift in the level of analysis from

traditional to modern epidemiologic and New Public Health approach. The significance

of the successful delivery of the New Public Health both at the level of society and

individual behavior (Halpin et al., 2010) justifies the intent of this dissertation on the need for further exploration of the pathopoiesis mechanism of tobacco use and FCH, the etiopathogenic role of gender and age. The unveiling of the "Precision Medicine Initiative" during the State of the Union Address of President Barack Obama on January 20, 2015, springboard the new effort of revolutionizing a new model of patient-powered research that could accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies. A near-term focus on cancers with a longer term aim to generate knowledge applicable to the whole range of health and disease are the two main components of this initiative (Collins & Varmus, 2015). In response to this initiative, Francis Collins, director of the National Institutes of Health and Harold Varmus, director of the National Cancer Institute acknowledge the near-term promise and the long-term benefits of precision medicine that not only requires global collaborations with related projects, but also motivating and attracting visionary scientists from many disciplines. The avidity of renewed debate on enhancing population health and well-being of the least-advantaged people will be dependent upon the success of this initiative with the assumption that precision medicine will contribute to the advancement of the health of the public and clinical practice. While Bayer and Galea (2015) question the full potential of precision medicine, Collins and Varmus (2015) highlighted what it could offer to the continued advancement of genomics and the new era of evidence-based disease-specific medical care without compromising patient privacy.

The downstream level of intervention of modern epidemiology through the provision of clinical preventive services such as screening and surveillance in concert

with public health programs could help explain the complex pattern of pancreatic cancer death (McLean, Williams & Lamont, 2013). The complementary role of outcomes research and epidemiology (Roger, 2011) can give way to improve the quality of care, as well as provide powerful and unique insights on efficient therapeutic approach. The practice of developing targeted interventions or medical treatments based on a person's environment, genetics and lifestyle are under the national microscope following the Precision Medicine Initiative (McGill, 2015). Precision medicine could readily reduce the incidence of PC by directing the focus on predictive testing on high-risk individuals before the likely onset of the disease. In the public health sphere, the advances in the genomic technology could identify those who unknowingly harbor a mutation in their genome, allowing for actionable interventions and a greater focus on disease prevention.

Summary

Strategies designed to improve the quality of life and survival rate of patients diagnosed with PC needs the continued progress in the identification of novel therapies (Hidalgo et. al, 2015). The genetic complexity of this lethal disease warrants the understanding of the Whole-exome and Whole-genome sequencing that will further advance the understanding of the etiopathogenic role of gender and age, in addition to pathopoiesis mechanism of smoking to PC/CTS-GA. Moreover, the dynamics of clonal diversification and selection are critical to understanding neoplastic progression and response to therapy (Greaves & Maley, 2012). Understanding and preventing therapeutic resistance lies in the continued research addressing the many fundamental questions in pancreatic cancer biology from the order of progression and mutation processes. The low

survival rates associated with this disease makes it critical to focus on improved outcomes and development of screening modalities to identify PC while the tumor is localized and amenable to surgical resection (Poruk et al., 2013). While Poruk et al. (2013) found that the incidence and population death rate from PC is high enough to consider population-level screening, the possible barrier to initiating screening strategy is the affordability and availability of a screening test with sensitivity and specificity of 90% that could identify PC patients at a resectable stage.

Recognized by the "Precision Medicine Initiative," personalizing treatment according to the presence of molecular targets could improve outcomes for patients with diseases with poor prognosis such as PC because of its genetic landscape (Chantrill et al., 2105). The different theories discussed in this chapter that embody the UPCC help explain GEIs justifying the gap being explored in this dissertation. Smoking cessation and acknowledgment of the value of personalized screening are cultural items that could induce positive socio-cultural transformation. Both in the context of traditional and modern epidemiology, equitable distribution of health-enhancing technologies, information, and treatments will help facilitate more rapid uptake and use of new health information among groups with lower SES, eventually reducing cancer mortality and achieving health equity (Rubin et al., 2014). Further research on the association of genetics and environmental interactions are critically important (Schenk et al., 2001). Likewise, Greaves and Maley (2012) asserted the promise of exciting clinical opportunities by focusing directly on the evolutionary adaptability of neoplasms and designing interventions to slow and direct, or control PC progression. The delivery of the

New Public Health both at the level of society and individual behavior (Halpin et al., 2010) justifies the importance of lifestyle change to reduce cancer risk, as well as its significance in prevention, and control of PC progression. Under the lens of Public Health and modern epidemiology—the study design, sampling, and statistical approach will be discussed in the following chapter.

Chapter 3: Research Method

In the previous chapter, current theory-driven literature was reviewed addressing

the specific components of pancreatic cancer epidemiology. In the review of the

literature, I also examined the different risk factors, the significance of screening and

surveillance, and the importance of genetic sequencing in defining the genetic blueprint

of pancreatic cancer. Given the new opportunities created by recent genetic discoveries to

improve the understanding of the molecular summation of pancreatic neoplasms, the

outcome of this study could provide a meaningful addition to the existing body of

knowledge on early detection and personalized treatment. To the best of my knowledge,

the etiologic risk factors within hierarchical levels, bridging the gap between individual,

macroenvironmental, and biologic levels, have not been examined under the lens of

modern epidemiology and public health. The gap on the modification effect of smoking,

age, and gender of individuals with CPG justified the intent of this study. A theory-driven

approach, as argued by Chen and Rossi (1983), will compensate for shortcomings of

research designs that do not meet the high standards of a randomized controlled

experimental model.

According to Lynch and Rebbeck (2013), most multilevel studies lack a focus on

the relationship between macroenvironment and individual-level factors, and the

traditional research on macroenvironment or individual-level factors remains broadly

defined without accounting for the PC genomic landscape. Lynch and Rebbeck

highlighted the need for full integration of biologic level elements with

macroenvironment and individual-level factors. Although smoking is strongly associated

with PC, most smokers will not be diagnosed with the disease. On the other hand, inherited mutations have a lower to high lifetime risk; some carriers may never be diagnosed, even at an advanced age. Considering that risk factors assessed in isolation and identified by a standard approach may not produce an in-depth evaluation of the complex multifactorial causes of PC, I focused on exploring the etiopathogenesis of the disease based on EGBIs at an individual level (smoking) and biologic level (inherited susceptibility variants). This approach supported the cumulative effects innards and across levels, or within at least two ways (see Table 3). The study design, sample, and analytic approach are addressed in this chapter.

Table 3

Hierarchical Level Definitions

Level	Sublevel	Factors at this level can serve as:
Macroenvironment	• Health policy (national, state, local • Community, neighborhood • Social and built environment • Practice setting and care providers • Family and social support	• Exposures that affect individual risk factors • Exposures that affect biologic processes • Contextual variables (Rebbeck et al., 2010)
Individual	• Behaviors • Exposures • Psychologic determinants • Socioeconomic factors	• Exposures leading to disease • Intermediate between the macroenvironment and disease
Biologic	• Tissue • Cell • Somatic genome • Inherited genome	• Processes leading to disease • Intermediates and biomarkers reflecting the relationship between macroenvironmental and individual factors

Note. From "Context-dependent effects of genome-wide association study genotypes and macroenvironment on time to biochemical (prostate-specific antigen) failure after prostatectomy" by Rebbeck et al., 2010, *Cancer Epidemiology Biomarkers & Prevention*, *19*(9), 2115-2123.

Study Design and Approach

The causality of tobacco-related mutagenic risk factors and the correlation

between gender and age and CPG will not only raise awareness of the significance of

cancer risk screening and counseling but will also increase the understanding of

environmental, genetic, and biodemographic interaction (EGBI) contributing to the

development and progression of PC. The results of this study may be used to promote

lifestyle change in reducing cancer risk. Improving the perceived corollary of individuals

with inherited genes and quality of life during the expression or final stage of the disease

is dependent on the favorable adjustment of behavioral risk factors. The intent of this

study was to explore the association between smoking, gender, and age in individuals

with CPG. I used a cross-sectional design to determine the prevalence of pancreatic

cancer and CTSG-A among smokers to answering the research questions:

RQ1: Is cigarette smoking associated with the etiopathogenesis of pancreatic

cancer and cancer types with shared gene association (CTSG-A)?

H_{01}: Smoking level has no correlation with prevalence of PC and CTSG-A.

H_1: Smoking can increase the risk of PC and CTSG-A.

RQ2: Is there a relationship between the combined role of age and gender in the

etiopathogenesis of PC and CTSG-A?

H_{02}: Age and gender have no correlation with prevalence of PC and CTSG-A.

H_2: Age and gender are correlated with the prevalence of PC and CTSG-A.

The overall risk of nonsmokers remains elevated in former smokers for up to 10

years or more, although smoking cessation lowers this risk of PC by up to 50% (Iodice et

al., 2008; Macleod & Chowdhury, 2006). The potential association of smoking, gender, and age as predictors of the outcome variable (PC/CTSG-A) were explored using a cross-sectional design. The sample size was determined using G*Power (Version 3.1.9.2). Given that estimating joint and marginal probabilities was not possible, investigating independence of D (PC) and E (Exposure: Smokers in association with PC/CTSG-A) nonsmokers with PC and CTSG-A was still possible. Secondary data were recoded and randomized using IBM Statistical Package for the Social Sciences (SPSS, Version 23, 64-bit edition). Although logistic regression makes no assumptions about the distributions of the predictor variables (smoking, gender, age), ordinal modeling was the fundamental property of the design of this study to test whether smoking level and age are effect modifiers to inherited genes or combined causative predictors in the induction and promotion of PC and CTSG-A. Regression procedures were used to examine the role of smoking in driving the initiation and progression of the disease in individuals with CPG (see Schaal, Padmanabhan & Chellappan, 2015). The odds of correlation or its combined interaction were examined using ordinal regression analysis.

According to Knol and VanderWeele (2012), the gap on presenting the analysis of effect modification and interaction showed that only 11% of cohort studies and case-control studies presented individual effects of both exposures and the joint effect of both exposure; therefore, it was necessary to assess overall interaction measures. The intent of this dissertation was to explore whether smoking (Q) contributed to the increased risk among individuals with FCH or CPG (E) on PC (D), where Q, D, and E were categorical/ordinal. Given the importance of presenting sufficient information and

drawing a statistically significant conclusion, I adopted the recommendations of Knol and VanderWeele and included OR and RR. Given that quantitative interaction is sometimes referred to as synergism or antagonism, interaction or its combined association was explored, which may be of public health interest considering that the effect of CPG as the primary exposure (see Figure 3) may vary across the subgroup (smokers, gender, age) and could give light to the significance of surveillance and early screening and the importance of behavioral change.

The dependent variable under Level 1 or Category 1 in this dissertation comprised cancer types with P16(CDKN2A) and PRSS1 mutations. Known as cyclin-dependent kinase inhibitor 2A (CDKN2A gene), p16 gene mutations occur in PC with 10-20% approximate risk and 20-34 times greater than that reported in any other tumor type (see Tables 1 and 2). Numerous additional studies have indicated a high frequency of p16 deletion in melanoma, esophageal, lung, pancreas, mesothelioma, bladder, head, and neck, breast, acute lymphocytic leukemia, brain, osteosarcoma, ovarian, and renal cell lines (Rocco & Sidransky, 2001). The mutations in the serine protease 1 gene or PRSS1 (Yi et al., 2016) were found to be a major factor of PC according to Zeng et al. (2011), with 50% approximate risk and 25%-40% risk by age 70 according to Lowenfels et al. (1997). The cancer types that were included as part of this category were pancreatic, melanoma, esophageal, leukemia, lung, bladder, renal, brain, osteosarcoma (bone), and cancer of the head and neck.
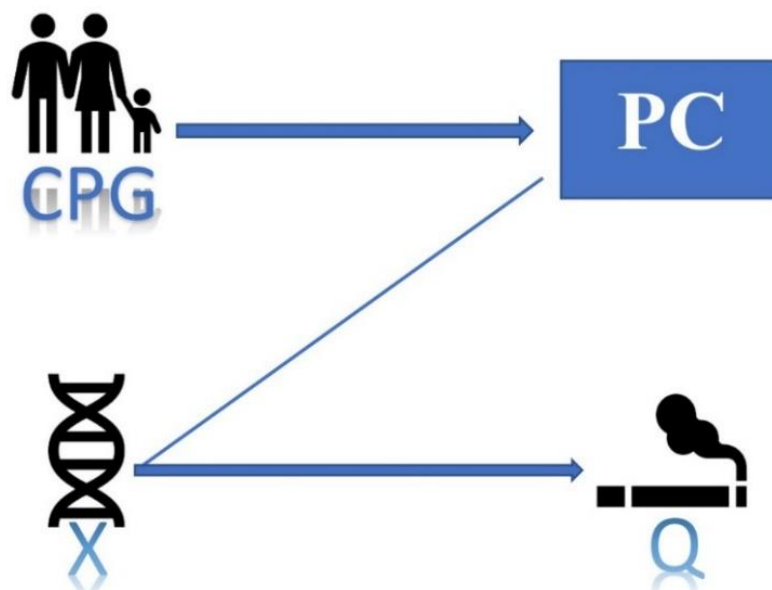
Figure 3. Q = Smoking, X = Genetic syndrome and associated gene(s), CPG (E), PC (D).

Level two or category two includes cancer types with BRCA1, STK11, and LKB1 mutations. While p16 is related to breast cancer, BRCA1 is two times to have a relative risk of PC, with higher risk by age 70. The human LKB gene (official HUGO symbol, STK11) encodes a serine/threonine protein kinase that is defective in patients with Peutz-Jeghers syndrome (PJS). Mutations occur particularly in lung and colorectal cancer (Launonen, 2005). The cancer types that are considered to be part of this category are breast, ovarian, and prostate cancer.

Level three or category three are composed of cancer types with bMLH1, and bMSH2 mutations. While the risk by age 70 is <5%, hereditary cancer syndromes that infer high cancer risks, require intensive cancer surveillance (Pearlman et al., 2017). It was suggested by Pearlman et al. that given the high frequency and broad spectrum of mutations, genetic counseling and testing are highly recommended. The cancer types in this category are endometrial, colorectal, and stomach cancer.

Setting and Sample

The secondary data in this study was from the 2014 Behavioral Risk Factor Surveillance System (BRFSS). Following the standards suggested for secondary analysis, descriptive and ordinal logistic regression will be performed (see Figure 4).
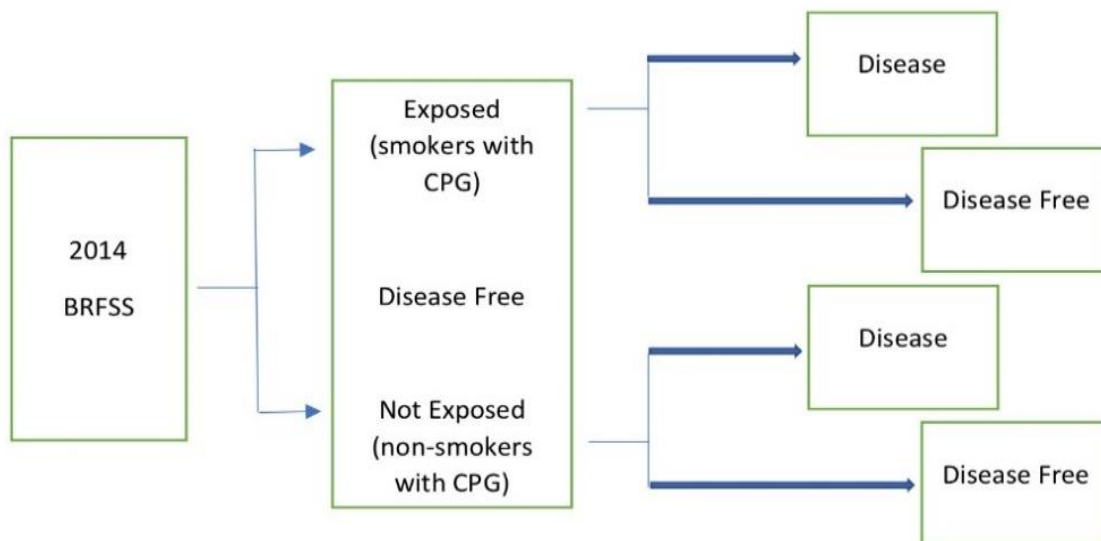
Figure 4. Epidemiologic data processing tree. (Based on the 2014 BRFSS and hypothetical conceptual cohort).

Description of the Study Population

The population for the study was defined as participants of the 2014 BRFSS survey. Subject selection criteria were set narrowly, by selecting specifically those who smoke and do not smoke with PC/CTSG-A (survivorship module), versus non-smokers with PC/CTSG-A. Subjects with PC/CTS-GA are those identified with inherited susceptibility variants (Table 1, Table 2). Association between smoking, age, gender, PC, and PC/CTSG-A are explored using hypothetical conceptual cohort. A hypothetical

conceptual cohort is defined as participants from the 2014 BRFSS survey who qualified as high-risk based on the level of smoking.

Sampling: Power Analysis

In this dissertation, like any cancer research or any other studies, the calculation of the sample size is critical, as well as the equal chance of every individual surveyed in the 2014 BRFSS in a target population to be included in the sample. It is important to remember that while random sampling is the gold standard of a sampling strategy, random sampling does not describe the sample or its size as much as it describes how the sample is chosen (Kadam & Bhalerao, 2010). Integral in generating ethically and scientifically sound results is to calculate the optimum number of required sample. Given the calculation of adequate sample size is pivotal, it is essential to remember that both the practicality of testing methodology and the statistical significance of the sample size are similarly critical. According to Kadam & Bhalerao (2010), the sample size for any study is dependent upon the power of the study, expected sample size, an acceptable level of significance, standard deviation and underlying event rate in the population. The "level of significance" in this dissertation is a significant p-value of <0.05. A power analysis (computed a priori: required sample size – given α, power, and effect size) was performed to estimate the effect size using G*Power (Version 3.1.9.2). While in large studies, the power is occasionally set at 90% to reduce the 10% possibility of a "false negative" result, I will accept a power of 80% with a total sample size of 116 (see Figure 5). However, the sample size of 116 after power analysis (PA) failed the ordinal logistic

regression assumptions; therefore, the remaining sample after data cleaning was utilized in this dissertation.
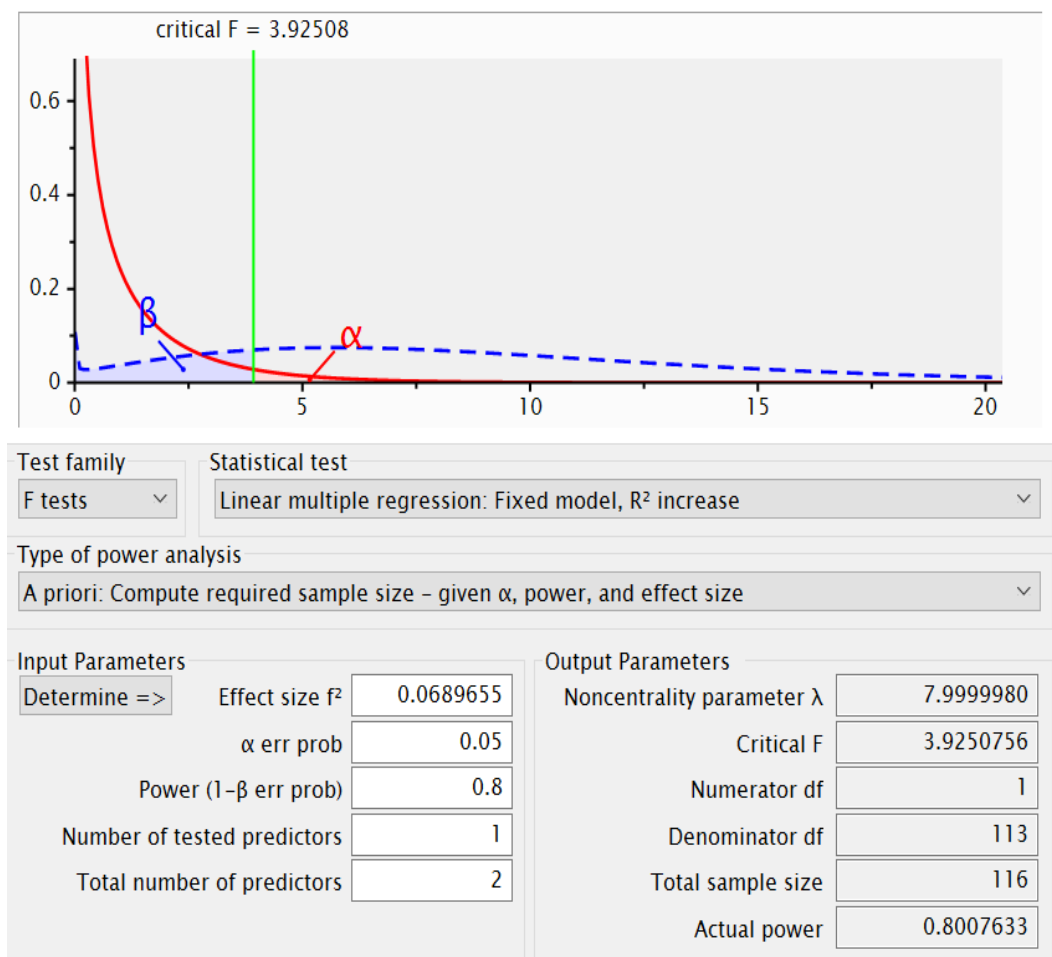
Figure 5. Power analysis.

Instrumentation and Materials

Conceding the fact that the sample and source of the secondary data already discussed and defined in this chapter, I would direct the focus to the instrumentation and materials required to conduct this dissertation. A description of the processes, dataset, and data collection tools is discussed.

Eligibility Criteria, Data Set, and Data Collection Tools

Subjects were selected at random and re-coded after I received IRB approval

(approval number 12-19-16-0390363). Variables in the data sets are identified under the

core section (tobacco, gender, age), "cancer survivorship" module of 2014 BRFSS

survey. Relevant data was kept using data storage device (USB flash drive), a backup

copy was uploaded to Microsoft OneDrive (Version 8.17.7).

Assessment of the Reliability and Validity of the Data

The key assumptions of this dissertation are strengthened by the reputation of the

Behavioral Risk Factor Surveillance System (BRFSS) as the nation's premier system of

collecting data on health-related behaviors, preventive services use and chronic health

conditions. While the causes of most PC remain unclear with a 5-10% run in families, the

reliability and validity of BRFSS data will help justify the significance of expanded

BRFSS, highlighting the need for adding cancer specific modules. Such modules could

help connect the association of modifiable risk factors and shared genes in the initiation

of cancer development.

Data Collection and Analysis

Data sets of 2014 BRFSS survey was obtained using a data storage device (USB

flash drive), and a backup copy was uploaded online using Microsoft OneDrive (Version

8.17.7). Extracted data will be exported, and re-coded using IBM Statistical Package for

the Social Sciences (SPSS, Version 23, 64-bit edition). Biologically plausible

relationships between smoking, gender, and age in the initiation and progression of PC is

quantified using regression methods. While it is relatively easy to consider an additional

in regression models, only variables that are clinically meaningful were included in this study. Regression methods were used to assess and adjust for confounding, and determine whether there is effect modification, as well as simultaneously evaluate the relationships of risk factors (smoking, age, gender). Given that this study involves PC/CTSG-A, and more than one independent variables, ordinal logistic regression analysis was performed to assess confounding and effect modification. The impact of multiple risk factors (smoking, gender, age) is examined as opposed to focusing on a single risk factor. Two separate logistic regression analyses (see Table 18A-C) was conducted to assess differences in induction and promotion of pancreatic cancer/CTSG-A by gender and three age groups (<51, 52-69, 70>). According to Langkamp, Lehman, and Lemeshow (2010), the technique of dropping cases with missing data should be discouraged; but in this study, the sample size was big enough to drop missing attributes, and stratified sampling will optimize generalizability.

<div align="center">**Summary**</div>

The population for this study was defined as participants of the 2014 BRFSS survey. The study is a cross-sectional model to examine the association of smoking, age, and gender or its combined causality to individuals with PC/ CTSG-A. Secondary data was re-coded and randomized through stratification, and regression modeling was performed using IBM Statistical Package for the Social Sciences (SPSS, Version 23, 64-bit edition). Countering the threats to external and internal validity was guided by the consideration of the importance of generalizability of the research data, passing the assumptions of the statistical analysis used, and stratification to deal with possible

confounders. The result of this examination will not only bring to light the noteworthiness of cancer risk screening and counseling but additionally will expand the understanding of the evolution of PC/ CTSG-A. The expected promise of this study will give light to the importance of lifestyle change to reduce cancer risk, promote prevention, and control of PC progression. To the best of my knowledge, exploring the etiologic risk factors within hierarchical levels, bridging the gap between individual, macroenvironmental and biologic level has not been examined under the lens of modern epidemiology and public health. The findings of the study could support the importance of behavioral risk factor and their roles in reducing the prevalence of PC and CTSG-A, enhancing the late-stage quality of life.

Chapter 4: Results

The purpose of the study was to explore the association between smoking as a shared environmental factor in individuals diagnosed with pancreatic cancer (PC) and CTSG-A and risk of extrapancreatic malignancies. A cross-sectional design was used to assess the burden of the disease and the need for public health intervention, planning, and allocation of health resources. Although this study did not include a molecular epidemiological analysis or provide information about the cause and effect of smoking level and PC and CTSG-A (see Table 4B.2, Figure 7), the outcome could highlight the significance of cancer-specific modules either as part of optional modules or expanded BRFSS. The positive results of this study could establish a working hypothesis for a longitudinal study addressing cause and effect, and could guide future improvements in the cancer-specific BRFSS survey module or the development of a supernet epidemiology surveillance system (SESS). SESS could spur an initiative to combine the Surveillance, Epidemiology, and End Results Program (SEER), BRFSS, and other monitoring networks in a single integrated system. Using a cross-sectional design could determine the prevalence of PC/CTSG-A and other cancers influenced by a shared environmental factor (smoking), essential to answering the research questions:

RQ1: Is cigarette smoking associated with the etiopathogenesis of pancreatic cancer and cancer types with shared gene association (CTSG-A)?

H_{01}: Smoking level has no correlation with prevalence of PC and CTSG-A.

H_1: Smoking can increase the risk of PC and CTSG-A.

RQ2: Is there a relationship between the combined role of age and gender in the etiopathogenesis of PC and CTSG-A?

H_{02}: Age and gender have no correlation with prevalence of PC and CTSG-A.

H_2: Age and gender are correlated with the prevalence of PC and CTSG-A.

Although a cross-sectional cohort study is an underutilized design (Hudson, Pope, & Glynn, 2005), it could be used to assess the association between exposures (smoking history/level) and the development of PC and comorbid cancer types. Missing attributes were dropped after data cleaning, and stratified randomization was performed to achieve optimum representation of the survey population. Table 4A and Figure 6 shows the six states (Alaska, Iowa, Mississippi, Missouri, Nebraska, and Wisconsin) that used the "cancer survivorship" module of the 2014 Behavioral Risk Factor Surveillance System (BRFSS) survey. Instead of the suggested sample size from power analysis noted in Chapter 3, to achieve generalizable results I used the remaining sample size of Nebraska BRFSS data sets based on the distinct CTSG-A as compared to Alaska, Iowa, Mississippi, Missouri, and Wisconsin. To provide a good picture of probable associations between the dependent (PC and cancer types with S-GA) and independent variables (gender, sex, smoking history/level, age), I estimated the prevalence of the dependent variable grouped according to CTSG-A at a single point in time (see Table 4C). I conducted ordinal logistic regression after recoding cancer types by prevalence proportion (PP) and evidence for shared association with PC.

Table 4A

Cancer Survivorship BRFSS Module by State FIPS Code

		Frequency	Percent	Valid Percent
Valid	Alaska FIPS-2	431	6.0	6.0
	Iowa FIPS-19	1150	16.0	16.0
	Mississippi FIPS-28	608	8.5	8.5
	Missouri FIPS-29	1103	15.4	15.4
	Nebraska FIPS-31	3003	41.9	41.9
	Wisconsin FIPS-55	874	12.2	12.2
	Total	7169	100.0	100.0
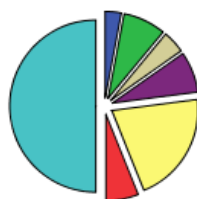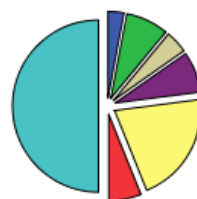
Figure 6. CA survivorship module participants based on state FIPS.

Table 4B.1

Case Processing Summary After Data Cleaning

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
CA Type Accdg. to SG-A * Respondents Gender	1691	100.0%	0	0.0%	1691	100.0%
CA Type Accdg. to SG-A * Four-Level Smoking Status	1691	100.0%	0	0.0%	1691	100.0%
CA Type Accdg. to SG-A * Three Age Group	1691	100.0%	0	0.0%	1691	100.0%

Table 4B.2

*Snapshot of CA Type According to SG-A*Independent Variables*

Respondents Gender	N	% of Total Sum	% of Total N
Male	692	36.9%	40.9%
Female	999	63.1%	59.1%
Total	1691	100.0%	100.0%
Four-Level Smoking Status			
Current-Smokes Everyday	124	7.0%	7.3%
Current-Smokes Some Days	36	2.0%	2.1%
Former Smoker	655	37.8%	38.7%
Never Smoked	876	53.1%	51.8%
Total	1691	100.0%	100.0%
Three Age Group			
<51	126	7.0%	7.5%
52-69	659	37.8%	39.0%
70>	906	55.2%	53.6%
Total	1691	100.0%	100.0%
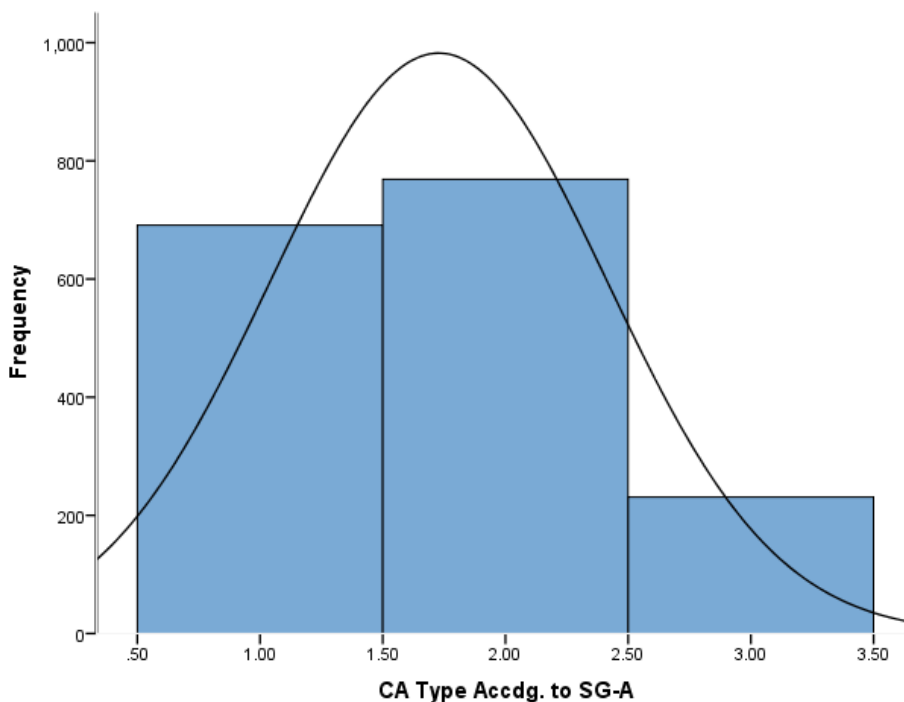
Figure 7. CA type according to SG-A.

Prevalence Proportion

PC prevalence proportion (PP) and PP of other cancer types were grouped based on shared association with PC/ CTSG-A (see Table 2) and computed to obtain the main outcome measure.

Table 4C

Frequency Table of CA Type According to SG-A

		Frequency	Percent	Valid Percent
Valid	P16(CDKN2A)/PRSS1	691	40.9	40.9
	BRCA1/STK11/LKB1	769	45.5	45.5
	bMLH1/bMSH2	231	13.7	13.7
	Total	1691	100.0	100.0

$$PP = \frac{\text{Number of cases in a defined population at one point in time}}{\text{Number of persons in a defined population at the same point in time}}$$

PP = P16(CDKN2A)/PRSS1 ÷ 1691

= 691/1691

= 0.4086 x 100

= 40.9%

PP = BRCA1/STK11/LKB1 ÷ 1691

= 769/1691

= 0.4547 x 100

= 45.5%

PP = bMLH1/bMSH2 ÷ 1691

= 231/1691

= 0.1366 x 100

= 13.7%

Analysis

Defining the gene and environmental factors that lead to the induction and promotion of the disease is essential to intervention and management development. Snapshot of the frequency of PC and cancer type with CTSG-A was generated in correlation to exposure variables using descriptive statistics. Frequency pattern of outcome variables allocated by recoded categorical numbers assessed in association with a dichotomous, polytomous, and continuous predictors (gender, smoking status, age).

The ordinal dependent variable (cancer type according to the shared gene association), and independent variables that are continuous, dichotomous and polytomous (age, gender, smoking status) in this study passed the first two ordinal logistic regression assumptions of my study design. There are four assumptions needed to be considered:

1. One dependent variable, measured at the ordinal level.

2. One or more independent variables that are dichotomous, continuous, categorical or ordinal.

3. There should be no multicollinearity.

4. The presence of proportional odds.

Before moving on to test the above assumptions, the PLUM ordinal regression procedure was run for the reliability of overall goodness-of-fit measures. Ideally, there should be no zero frequency to move on in interpreting and reporting the goodness-of-fit measures, or have 80% or more expected cell frequencies. The dataset before power analysis (PA) has 4 (5.8%) with zero frequencies, versus 69.4% with zero frequencies after power analysis. Therefore, the remaining sample size after data cleaning and re-coding (before PA) was used in this dissertation. Assumption "3" was confirmed by running linear regression procedure. Based on the coefficient table, tolerance values are greater than 0.1 (the lowest is .349) with all the variance inflation factors are much less than 10, indicative of zero multicollinearity problems.

Table 5

Multicollinearity Test: Coefficients[a]

		Collinearity Statistics	
Model		Tolerance	VIF
1	Respondents Gender	.933	1.072
	Three Age Group	.967	1.035
	Current-Smokes Everyday	.349	2.866
	Former Smoker	.361	2.768
	Never Smoked	.589	1.697
a. Dependent Variable: CA Type Accdg. to SG-A			

Given that the data set passed assumption "3," separate binomial logistic regression is performed, followed by PLUM, and GENLIN procedure. Assessed by a full likelihood ratio test to compare the fit of the proportional odds model to a model with varying location parameters, $X^2(5) = 6.497$ with a p-value of .261. The test of parallel lines is suggestive to passing the assumption of proportional odds (assumption 2), as noted in the difference between the models, and the p-value greater than .05 (.261).

Table 6

Test of Parallel Lines[a]

Model	-2 Log Likelihood	Chi-Square	df	Sig.
Null Hypothesis	191.698			
General	185.202	6.497	5	.261

The null hypothesis states that the location parameters (slope coefficients)
are the same across response categories.
a. Link function: Logit.

After running the PLUM-ordinal regression, there are 4 (5.8%) with zero frequencies; therefore having 94.2% expected cell frequencies is indicative of the reliability of overall goodness-of-fit measures. Both the Pearson and deviance goodness-

of-fit test was a good fit to the observed data with p-values >.05. The final model statistically significantly predicted the dependent variable over and above the intercept-only model, $X^2(5) = 99.090$ with a p-value < .001.

Table 7

Goodness-of-Fit

	Chi-Square	df	Sig.
Pearson	38.011	39	.515
Deviance	41.325	39	.369

Link function: Logit.

Table 8

Model Fitting Information

Model	-2 Log Likelihood	Chi-Square	df	Sig.
Intercept Only	290.788			
Final	191.698	99.090	5	.000

Link function: Logit.

While the "Tests of Model Effect" shows that smoking status has no significant effect on the prediction of developing PC and CTSG-A; gender is statistically significant predictor with p = .000, Wald X2(1) = 75.507. This predictor has a statistically significant effect on the prediction of PC/ CTSG-A induction and promotion.

Table 9

Tests of Model Effects

	Type III		
Source	Wald Chi-Square	df	Sig.
Gender	75.507	1	.000
Smoking Status	2.038	3	.564
Age	17.538	1	.000

Dependent Variable: CA Type Accdg. to SG-A

Model: (Threshold), Gender, Smoking Status, Age

The odds of male respondents developing PC and CTSG-A versus the female respondents is .418 (95% Cl, .344 to .509) with a statistically significant effect, X2 (1) = 75.507, p-value < .0005. An increase in age (expressed in years) was associated with an increase in the odds of developing the disease, with an odds ratio of 1.374 (95% CI, 1.184 to 1.595), Wald $\chi2(1) = 17.538$, p < .0005.

Table 10

GENLIN Procedure Parameter Estimates

Parameter		B	Std. Error	95% Wald Confidence Interval		Hypothesis Test			Exp(B)	95% Wald Confidence Interval for Exp(B)	
				Lower	Upper	Wald Chi-Square	df	Sig.		Lower	Upper
Threshold	[CAType_SG_A =1.00]	-.005	.1965	-.390	.380	.001	1	.980	.995	.677	1.463
	[CAType_SG_A =2.00]	2.303	.2061	1.899	2.707	124.874	1	.000	10.008	6.682	14.991
Male		-.872	.1003	-1.068	-.675	75.507	1	.000	.418	.344	.509
Female		0ª	.	.	.	.	.	.	1	.	.
Current-Smokes Everyday		-.190	.1867	-.556	.176	1.039	1	.308	.827	.573	1.192
Current-Smokes Some Days		-.326	.3305	-.974	.322	.973	1	.324	.722	.378	1.380
Former Smoker		-.073	.1028	-.275	.128	.507	1	.476	.929	.760	1.137
Never Smoked		0ª	.	.	.	.	.	.	1	.	.
Age		.318	.0759	.169	.467	17.538	1	.000	1.374	1.184	1.595
(Scale)		1ᵇ									

Dependent Variable: CA Type Accdg. to SG-A

Model: (Threshold), Gender, Smoking Status, Age

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

Table 11

*CA Type Accdg. to SG-A * Predicted Response Category Crosstabulation*

			Predicted Response Category		
			P16(CDKN2A/PRSS1	BRCA1/STK11/LKB1	Total
CA Type Accdg. to SG-A	P16(CDKN2A)/PRSS1	Count	379	312	691
		% within CA Type Accdg. to SG-A	54.8%	45.2%	100.0%
	BRCA1/STK11/LKB1	Count	264	505	769
		% within CA Type Accdg. to SG-A	34.3%	65.7%	100.0%
	bMLH1/bMSH2	Count	67	164	231
		% within CA Type Accdg. to SG-A	29.0%	71.0%	100.0%
Total		Count	710	981	1691
		% within CA Type Accdg. to SG-A	42.0%	58.0%	100.0%

Table 12.1

*Prev1*Variables in the Equation*

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Male (1)	.905	.106	72.231	1	.000	2.472
	Smoking Status			3.343	3	.342	
	Current-Smokes Everyday (1)	.262	.200	1.730	1	.188	1.300
	Current-Smokes Some Days (2)	.341	.349	.952	1	.329	1.406
	Former Smoker (3)	.144	.112	1.658	1	.198	1.155
	Age	-.349	.082	18.169	1	.000	.705
	Constant	.017	.210	.007	1	.935	1.017

a. Variable(s) entered on step 1: Gender, Smoking Status, Age.

Table 12.2

Prev1*Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	99.758	5	.000
	Block	99.758	5	.000
	Model	99.758	5	.000

Table 12.3

Prev1*Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	2187.683[a]	.057	.077

a. Estimation terminated at iteration number 3 because parameter estimates changed by less than .001.

Positive Predictive Value: Prev1

$=100 \times (314/248+314)$

$= 100 \times (314/562), =100 \times 0.5587$

$= 55.9\%$. That is, of all cases predicted as having P16(CDKN2A)/PRSS1 genes that could directly cause the initiation of PC and other CTSG-A, 55.9% were correctly predicted.

Negative Predictive Value: Prev1

$= 100 \times (752/752+377)$

$= 100 \times (752/1,129)$

$= 100 \times .6660$

= 66.6%. That is, of all cases predicted as not having the genes directly responsible for the development of PC and other CTSG-A, 66.6% were correctly predicted.

Table 12.4

Prev1*Classification Table[a]

Observed			Predicted		
			Prev1		
			BRCA1/STK11/LKB1/bMLH1/bMSH2	P16(CDKN2A)/PRSS1	Percentage Correct
Step 1	Prev1	BRCA1/STK11/LKB1/bMLH1/bMSH2 = No	752	248	75.2
		P16(CDKN2A)/PRSS1 = Yes	377	314	45.4
	Overall Percentage				63.0

Table 12.5

Prev2*Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Male (1)	-.553	.105	27.881	1	.000	.575
	Smoking Status			3.562	3	.313	
	Current-Smokes Everyday (1)	-.250	.198	1.584	1	.208	.779
	Current-Smokes Some Days (2)	-.109	.346	.100	1	.752	.896
	Former Smoker (3)	-.179	.109	2.702	1	.100	.836
	Age	.242	.080	9.121	1	.003	1.274
	Constant	-.467	.208	5.063	1	.024	.627

a. Variable(s) entered on step 1: Gender, Smoking Status, Age.

Table 12.6

Prev2*Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	44.897	5	.000
	Block	44.897	5	.000
	Model	44.897	5	.000

Table 12.7

Prev2*Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	2285.464[a]	.026	.035

a.   Estimation terminated at iteration number 3 because parameter estimates changed by less than .001.

Positive Predictive Value: Prev2

= 100 x (395/353+395)

= 100 x (395/748)

= 100 X .5280

= 52.8%. That is, of all cases surveyed to have PC and other CTSG-A, the probability of

having the BRCA1, STK11, and LKB1 genes have 52.8% positive predictive value.

Negative Predictive Value: Prev2

= 100 x (569/569+374)

= 100 x (569/943)

= 100 x .6033

=60.3%. That is, of all cases predicted as not having SG-A, 60.3% were correctly

predicted.

Table 12.8

Prev2*Classification Table[a]

			Predicted		
			Prev2		
Observed			P16(CDKN2 A)/PRSS1/b MLH1/bMS H2	BRCA1/STK11/ LKB1	Percentage Correct
Step 1	Prev2	P16(CDKN2A)/PRSS1/bM LH1/bMSH2 = No	569	353	61.7
		BRCA1/STK11/LKB1 = Yes	374	395	51.4
	Overall Percentage				57.0

a. The cut value is .500

Table 12.9

Parameter Estimates and Odd Ratios

		Prev1			Prev2		
	Independent Variable	B	Sig.	Exp(B)	B	Sig.	Exp(B)
Step 1[a]	Male (1)	-.553	.000	.905	.905	.000	2.472
	Smoking Status		.313			.342	
	Current-Smokes Everyday (1)	-.250	.208	.262	.262	.188	1.300
	Current-Smokes Some Days (2)	-.109	.752	.341	.341	.329	1.406
	Former Smoker (3)	-.179	.100	.144	.144	.198	1.155
	Age	.242	.003	-.349	-.349	.000	.705
	Constant	-.467	.024	.017	.017	.935	1.017

a. Variable(s) entered on step 1: Gender, Smoking Status, Age.

Summary

The effect of tobacco use, age, and sex in the etiopathogenesis of PC and CTSG-A was assessed using cumulative odds ordinal logistic regression with proportional odds. While the results of this study supported the null hypotheses that smoking has no correlation with the prevalence of PC and CTSG-A as confirmed by the GENLIN parameter estimates, both gender and age are statistically significant predictors with <.05 p-values. The odds of male respondents developing PC and CTSG-A versus the female respondents is .418 (95% Cl, .344 to .509) with a statistically significant effect, X2 (1) = 75.507. The odds ratio of 1.374 (95% CI, 1.184 to 1.595), Wald χ2(1) = 17.538 is suggestive to the increased probability of developing the disease as the person reach the age between 62 and 69 years of age. The findings of this dissertation support the results of Ellison (2017) that the age-specific pattern of PC tends to be at age 60, and 4 in 5 cases during 2011 to 2013 were 70 and older. Likewise, separate binomial logistic regression analysis shows age was associated with an increased likelihood of developing the disease. Analogous to the results of the ordinal logistic regression analysis, the odds of the male participants of the 2014 BRFSS survey is 2.472 times greater to develop the disease as opposed to female respondents. Further discussion of the results of this study and its implication for connecting the association of tobacco use, gender, and age in the initiation of PC and CTSG-A will be presented in chapter 5. In addition to a discussion of the positive social impact, the following chapter will review potential lines of inquiry for future research.

Chapter 5: Discussion, Conclusions, and Recommendations

Overview

Pancreatic cancer has become the third leading cause of cancer-related death, with little improvement in mortality and outcomes despite decades of research (Dreyer, Chang, Bailey, & Biankin, 2017; Lucas et al. 2016). The need to acknowledge continued research is critical to recognize the importance of establishing meaningful, evidence-based risk prediction models that could be applied in clinical settings to improve the accuracy of early identification of premalignant lesions as part of a personalized therapeutic approach. Although regular smoking was confirmed as a significant risk factor in both sexes by Andersson, Wennersten, Borgquist, and Jirström (2016), the association between smoking intensity and duration was not statistically significant in the current study. Drawing conclusions about smoking and family history can be complicated because both commonly track in the same family and it is difficult to differentiate the genetic component from the carcinogen exposure using BRFSS data. The likely impact of improved understanding of the etiopathogenic role of gender and age and the pathopoiesis mechanism of smoking to PC and CTSG-A prompted the current study.

A cross-sectional design was used to understand environmental, genetic, and biodemographic interactions (EGBIs) and generate hypotheses for future research. The purpose of the study was to establish the existence or absence of correlation between tobacco use, gender, and age in the etiopathogenesis of PC/CTSG-A, with the intent of enhancing the understanding of EGBIs in disease evolution (induction, promotion, and expression periods). The following research questions and hypotheses were addressed:

RQ1: Is cigarette smoking associated with the etiopathogenesis of pancreatic cancer and cancer types with shared gene association (CTSG-A)?

H_{01}: Smoking level has no correlation with the prevalence of PC and CTSG-A.

H_1: Smoking can increase the risk of PC and CTSG-A.

RQ2: Is there a relationship between the combined role of age and gender in the etiopathogenesis of PC and CTSG-A?

H_{02}: Age and gender have no correlation with the prevalence of PC and CTSG-A.

H_2: Age and gender are correlated with the prevalence of PC and CTSG-A.

Cumulative odds ordinal logistic regression with proportional odds was run, and two separate binomial logistic regression analyses were performed to determine the effects of age, gender, and smoking level among participants with P16(CDKN2A)/PRSS1 genes and BRCA1/STK11/LKB1 genes on the likelihood of developing PC and CTSG-A. After passing the first two ordinal logistic regression assumptions, the third assumption (zero multicollinearity) was confirmed by running the linear regression procedure. Based on the coefficient table, the tolerance values were greater than 0.1 (the lowest was .349), and all of the variance inflation factors were much less than 10, indicative of zero multicollinearity problems. The presence of proportional odds (Assumption 4) was assessed by a full likelihood ratio test. Results of the study indicated zero correlation between tobacco use and the prevalence of PC and CTSG-A. Both gender and age were statistically significant predictors of PC and CTSG-A evolution.

<center>**Discussion**</center>

Germline Genetic Alterations

Pancreatic cancer (PC) is a disease of inherited (germline) and somatic gene mutations (Maitra & Hruban, 2008). In the current study, cancer types of the 2014 BRFSS cancer survivorship module were grouped based on germline genetic alterations that had been recognized and summarized by Maitra and Hruban as having been associated with an increased risk of pancreatic cancer. Of the 28 cancer types surveyed in the 2014 BRFSS, there were 16 cancer types in the cancer survivorship module known to have a shared-gene association (SG-A). These 16 cancer types were grouped based on germline mutation genes to establish levels of the dependent variable: 1= P16(CDKN2A)/PRSS1, 2 = BRCA1/STK11/LKB1, 3 = bMLH1/bMSH2.

Multicollinearity and the Increased Likelihood of Developing the Disease

I created dummy variables to test for the assumption of multicollinearity, and created dichotomous cumulative categories of the levels of the dependent variable required for the assumption of proportional odds and to run diagnostics that were critical in setting up the data set to run an ordinal logistic regression. Dichotomous cumulative categories (Prev1, Prev2) of the levels of the dependent variable were created and recoded as follows:

Prev1 = 0 (all other values: BRCA1/STK11/LKB1/bMLH1/bMSH2), 1 (P16(CDKN2A)/PRSS1);

Prev2 = 0 (all other values: P16(CDKN2A)/PRSS1/bMLH1/bMSH2), 1 (BRCA1/STK11/LKB1).

The logistic regression model was statistically significant, $\chi2(5) = 99.758, p <$ .0005. The model explained 7.7% (Nagelkerke R2) of the variance in the outcome variable and correctly classified 63.0% of cases. Sensitivity was 45.4%, specificity was 75.2%, positive predictive value was 55.9%, and negative predictive value was 66.6%. Of the three predictor variables, gender and age were statistically significant. Increasing age was associated with an increased likelihood of developing the disease. Gender with a *p* value of .000 and age with a *p* value of .000 added significantly to the model/prediction compared to smoking status. Male respondents had 2.472 times greater odds to develop the disease as opposed to female respondents. Among participants with BRCA1/STK11/LKB1 genes, binomial logistic regression analysis indicated the effects of age, gender, and smoking level on the likelihood of developing PC and CTSG-A. The logistic regression model was statistically significant, $\chi2(5) = 44.897, p < .0005$. The model explained 3.5% (Nagelkerke R2) of the variance in the outcome variable and correctly classified 63.0% of cases. Sensitivity was 51.4%, specificity was 61.7%, positive predictive value was 52.8%, and negative predictive value was 60.3%. As in participants with P16(CDKN2A)/PRSS1 genes, two predictor variables (gender and age) among participants with BRCA1/STK11/LKB1 genes were statistically significant. Increasing age was associated with an increased likelihood of developing the disease. Gender with a *p* value <.0005 and age with a *p* value of <.0005 added significantly to the model/prediction compared to smoking status. Male respondents had a 57.5% likelihood to develop the disease, a statistically significant effect, X2 (1) = 75.507, p-value < .0005 with .418 (95% Cl, .344 to .509) times that of female respondents.

Proportional Odds Model and Cumulative Odds Ordinal Logistic Model

Cumulative odds ordinal logistic regression with proportional odds was run to determine the effect of tobacco use, age, and gender in the etiopathogenesis of PC/CTSG. The assumption of proportional odds was met, as assessed by a full likelihood ratio test comparing the fit of the proportional odds model to a model with varying location parameter, $X2(5) = 6.497$ with a p value of .261. The percentage of cells with zero frequency was 5.8%; therefore, 94.2% of expected cell frequencies were indicative of the reliability of overall goodness-of-fit measures. Both the Pearson and deviance goodness-of-fit indicated that the model was a good fit to the observed data, $X2(39$ [Pearson], 39 [deviance]) $= 38.011$ [Pearson], 41.325 [deviance], with p values of .515 and .369, respectively. The final model significantly predicted the dependent variable over and above the intercept-only model, $X2(5) = 99.090$ with a p value $< .001$. Although the GENLIN parameter estimates showed that smoking status was not significantly associated with the outcome, both gender and age were significant predictors. The odds ratio of male respondents developing PC and CTSG-A compare to female respondents was .418 (95% Cl, .344 to .509) with a statistically significant effect, $X2 (1) = 75.507$, p value $< .0005$.

Although the Pearson chi-square results showed Prev1 and Prev2 smoking level was statistically significant, cumulative odds ordinal logistic regression showed higher p values compared to age and gender. An increase in age (expressed in years) was associated with an increase in the odds of developing PC/CTSG-A, with an odds ratio of 1.374 (95% CI, 1.184 to 1.595), Wald $\chi2(1) = 17.538$, $p < .0005$. Likewise, the Tests of

Model Effect showed that smoking status was not a significant predictor. The

respondent's gender was a statistically significant predictor of PC/ CTSG-A with a *p*

value <.05, Wald X2(1) = 75.507 indicating statistically significant predictor effect.

Limitations

When I started this study, my initial intent was to analyze data from Johns

Hopkins University National Familial Pancreas Tumor Registry (NFPTR) to address my

research questions and hypotheses. The data-driven approach and the research question

approach are the two general approaches for analyzing existing data (Cheng & Phillips,

2014). According to Cheng and Phillips (2014), these two methods are often used jointly

and interactively. Using NFPTR secondary data, the research question approach was

more appropriate, but because of the time and challenges involved in establishing an

inter-institutional relationship, I decided to move on with analyzing the data from the

2014 BRFSS. Although my approach remained research question driven, I also

incorporated a data-driven approach and revised my research questions and hypotheses so

they could be answered by the available data. However, BRFSS data are not as good and

thorough as NFPTR data. This may have influenced the validity of my findings.

In secondary data analysis, there are some limitations that need to be addressed.

Firstly, missing values that could be caused by skip patterns in long and comprehensive

surveys like BRFSS are common to reduce interviewer-interviewee burden and burn-out

by skipping a group of questions that are not relevant for a particular respondent. After

data cleaning, the variables in this dissertation are the only data that can generate

statistically significant results and pass the assumptions of the statistical model used in

the analysis. Secondly, while using both 'data-driven' approach' and the 'research question-driven' approach, the limitations of using secondary data resulted in the mixed statistical outcome of the association of smoking to cancer evolution. Given that 51.8% of the respondents are non-smokers after data cleaning (see Table 4B.2) could explain why the results of non-parametric tests (Chi Square tests) are statistically significant (see Appendix D and E) compared to the results of the ordinal logistic regression. Lastly, given that probability sampling in this dissertation was done using stratified random sampling by framing the surveyed cancer types by shared genes association, it is hard to draw conclusions about smoking and family history in association to the genetic component from the carcinogen exposure. This research endeavor can be initiated using a registry data from NFPTR, but not with current BRFSS modules. Therefore, it critical to revise existing BRFSS modules, adding cancer specific modules with the history of cancer mortality within the family tree genealogy that includes whole-genome sequencing (WGS) information. Such revision could compliment future studies using registry data, and the development of the epidemiological-genealogical tree, complimentary to cancer specific risk history diagnosis scale.

Implications for Social Change

Precision medicine may not be synonymous with whole-genome sequencing (WGS), but the application of genomic technologies could promote positive social change on embracing the promise of WGS in healthy people. The key strategy in using WGS is to tailor care to minimize harm to individuals through anticipatory counseling in the face of the untargeted nature of the potential findings (Lindor, Thibodeau, & Burke,

2017). This 2017 study further stated that the utility of "next-generation" sequencing had been found to establish the diagnosis for hundreds of genetic disorders, to assess pharmacogenomic variants, and to identify treatable targets within malignant neoplasms. Given that gender and age are the statistically significant predictors in this dissertation versus tobacco use, it is paramount to discuss its role, parallel to the overall recognition of the WGS's potential benefits as the ultimate genetic test. Benefits include the satisfaction in knowing more about one's genome, or the with WGS in healthy people may include disappointment in how little is interpretable (Dewey et al., 2014; Lindor et al., 2015).

In addition to smoking cessation discussed in previous chapters, the results of this dissertation have several implications for social change, such as recognizing cultural values in developing effective communication structured from the statistically significant etiopathogenic role of gender and age in the development of PC and CTSG-A. This will give a clear understanding of what to ask, and what actions to take, allowing the family to openly explore treatment alternatives during the terminal phase of the illness (Ballard-Reisch & Letner, 2003). Primary prevention must be prioritized as an integral part of global cancer control. According to Vineis et al., (2014), primary prevention has several advantages: the effectiveness could have benefits for people other than those directly targeted, avoidance of exposure to carcinogenic agents is likely to prevent other non-communicable diseases, and the cause could be removed or reduced in the long term through regulatory measures against occupational or environmental exposures such as environmental tobacco smoke (ETS). However, no regulatory standards nor advanced

innovations could change the hearts and minds of the general population unless evidence-based studies support it. Social change will be dependent upon the continued dissemination of current cancer research built on integrative social molecular pathological epidemiology (MPE). While remarkable progress has been made in the last decade in advanced technology and new methods for biologic measurements; the reductionist approach of modern epidemiology often remits the principal causes of disease. Pearce (1996) argue that epidemiology must reintegrate itself into public health and must rediscover the population perspective. However, while the new paradigm of downstream (individual) approach could produce a lifestyle approach to social policy, the cumulative outcome of research in cancer epidemiology could equate positive implications to population health.

It is important to acknowledge the promise of the holistic approach to improving health behaviors through health literacy among vulnerable groups that were found to be an increased risk of developing PC. Complimentary to the statistical outcome of this dissertation, Clouston, Manganello, and Richards, (2017) found that women have higher health literacy than men. Moreover, given that an increase in age was associated with the odds of developing PC/CTSG-A, a holistic approach should be focused not only on the adults but also the younger members of families and communities (Clauston et al., 2017). According to Kumar et al. (2012), the attainment of the highest possible standard of health depends on a comprehensive, holistic approach which goes beyond the traditional curative care, involving communities, health providers, and other stakeholders. The challenges due to the changing scenarios such as demographic and epidemiological

transition, proven by the statistical outcome of this dissertation, amplifies the need for newer, innovative approaches that are multisectoral, adequately funded, evidence-based health promotion program with community participation. The global acceptance that health and social well-being are determined by many factors which are outside the health system that requires modification of the complex socioeconomic determinants of health, targeting the complex socioeconomic and cultural changes at family and community levels (Kumar and Preetha, 2012).

The argument on the gene-environment interaction paradigm to genome-wide studies in relation to the development of a public issue was discussed in the 2014 study of Boardman et al., highlighting the importance of integrating social and genetic perspectives in enhancing findings for both biologically and socially focused research such as the causality of active and passive smoke exposure to lifetime risk of a fetus to develop a lethal disease like PC. For decades, behavior geneticists have been working to disentangle the genomic component of family risk from the social and behavioral component. According to Boardman et al., understanding the genomic component in combination with specific environmental contexts could provide the pertinent information about an individual's likelihood of exhibiting a particular behavior at a given time, critical not only to social and genetic epidemiologists, but to the understanding of the causes, modifiable behavioral risk and adjustable predictors in the development of the disease. New evidence for genetic influences on most health behaviors, new statistical methods, and new genetic data sources could help confirm the significance of

environmental influences on individual's genetic composition that could be contingent on the social environment in which one resides, works, and plays.

The mutually advantageous conjunction of viewing positive social change in cancer epidemiology beyond genetics and social inequalities, the continued technical advancement to gauge host resistance at a molecular level before the onset of disease and within the healthy social ecology will lead to human vitality and physiological resilience (Cole, 2013). Moreover, in combination with the conceptual advances of a network-level metagenomic approach to people's health, Cole (2013) emphasized its weight in accelerating the ongoing transformation of public health from a disease-reactive model to a more proactive and health-centered approach. While genome-wide analysis can hypothesize links to environmental sensitivity via biologically plausible networks (Duncan et al. 2010), positive social change is critical to the continued interest and openness in knowing about one's genetic makeup that holds sufficient information enough to construct a priori disease-specific genetic profiles (Boardman et. al, 2014).

Recommendations for Action

Cancer is a growing global problem and is increasing in the proportion of the burden among low income and middle-income countries. The pattern can be blamed on demographic change and to transition in risk factors, but can be preventable by present knowledge of risk factors. In early 2000, PC incidence rates have been approximately stable in many European countries, overall trends in USA, Japan, and Australia are likely to improve in the next future with more favorable trends among young adults from 30 to 49 years old (Bosetti et al., 2012b). Pancreatic cancer has the lowest 5-year relative

survival rate, and treatment for metastatic pancreatic cancer are minimally effective. Ma,

Siegel, & Jemal (2013) noted that the complex patterns about death rate trends for

pancreatic cancer remain unexplained by known risk factors. Given that there are only

20% of patients diagnosed with the disease are eligible for surgical resection (Spanknebel

& Conlon, 2000); it is paramount to rationalize the importance of the development of

public health policies designed in lowering the economic burden of the disease. Money

saved from reducing the overall economic burden of the disease could open up resources

and funding allocation to pursue other public health projects for the better good of the

many.

     Environmental tobacco smoke (ETS) is an example of environmental exposure

that has been associated with an array of adverse effects on health. Secondhand smoke,

referred to as ETS, contains many of the same carcinogenic compounds as the

mainstream smoke inhaled by active smokers (World Health Organization, International

Agency for Research on Cancer, 2004; Bao et al., 2009). Under the lens of public health,

quitting smoking could decrease the incidence of PC, by protecting vulnerable members

of the population. The rapid uptake and use of new health information among vulnerable

groups, and access to health-enhancing treatment and technologies will be dependent

upon the development and implementation of public health policies that include equitable

allocation of resources to every enclave of the community. While the past and current

research could help continue the improvement of the accuracy of passive smoking

measurement, it is critical for the continuance of applying the exposome concept to

environmental health problems. Research outcomes that help the drafting of amendments

to policies and approaches, built on existing policies such as cigarette labeling acts, smoking bans, and distribution of cessation tools will not only improve mortality level of the disease but population health as a whole.

One of the greatest challenges and opportunities for 2016 is to intensify the implementation of evidence-based path-breaking interventions in modifying major risk factors for chronic diseases such pancreatic cancer beyond genetics and social inequalities. According to Halpin et al. (2010), delivering interventions at the level of society using the paradigm of the New Public Health can change the environment, and individual behaviors through public health policy, and focus beyond genetics and social inequalities. It is critical to acknowledge the burden of PC and the assessment of the current state of research on this issue, shedding light on the critical significance of environmental epidemiology in protecting vulnerable subgroups of populations from environmental hazards and its causal association on induction and promotion of pancreatic cancer. The burden of chronic diseases such PC is often ignored on the public agendas at both the individual and community level, albeit most public health interventions focus on induction and promotion (Haplin et al., 2010). While the correlation of smoking is statistically significantly weak in this dissertation, the biggest single cause of cancer is tobacco use. Therefore, it is paramount to embrace the concept of precision medicine in integrating molecular pathology, epidemiology, and social science.

The evolving transdisciplinary field of molecular pathological epidemiology (MPE), could better connect the dots of the pathopoiesis mechanism of smoking and

shared genes in pancreatic cancer, as well as integrate molecular analysis into social epidemiology for deeper insights on social influences on pathogenic processes (Nishi et al., 2016). According to Colditz, Wolin, and Gehlert (2012), better implementation of lessons learned in this dissertation could contribute to achieving maximal possible cancer prevention, to counter the projected doubling of cancer cases diagnosed by 2050 (Edwards et al., 2002). While molecular window into the body could help guide public health interventions and social policies to more proactively address the general host resistance factors that seem to precipitate multiple diseases (Miller, Chen, & Cole, 2009), lessons learned from studies that link specific gene expression profiles to disease vulnerability could help gauge the toxicity of various social or geographic environments or the success of public policies and interventions (Cole, 2013). As some researchers argue the complexity of exploring the assumption that smoking and family history, both commonly track together in the same family and differentiating the genetic component from the carcinogen exposure may be difficult or even impossible without exploring its molecular window, or limited access to established registry data, it is important to consider revising current BRFSS cancer survivorship module. Such revision could open the opportunity for an inferential risk and cancer-specific profiles. Furthermore, an additional module on sleeping habits and patterns in Expanded BRFSS could connect the dot on its association with higher body weight or obesity that is known to be a behavioral risk factor in cancer evolution (Donohoe, Lysaght, O'Sullivan, & Reynolds, 2017).

The cloud created by the present administration's goals of the "FY 2018 skinny budget" that was widely condemned by scientists and public health advocates is the deep

cuts in medical research and health care (Lewis-Burke Associates, 2017). This initial

funding blueprint would weaken public health ad nauseam, as much of the health safety

net formed by the Department of Health and Human Services, the Centers for Medicare

and Medicaid Services, the Centers for Disease and Prevention (CDC), and the National

Institutes of Health (NIH). What can we do to offset the ramifications of the Trump

budget? The deplorable truth is that if this budget were enacted, will not only result in

cancers and diseases going undetected, but the future of scientists and academics who

work so hard to reverse mortality rate, and economic burden. Infectious diseases, and

current public health issues that include bioterrorism, and violent radicalization will not

be deterred by a proposed enhanced wall in our borders.

Recommendations for Future Research

One of the major obstacles confronting funding research and public health

projects is the failure to connect the dots between the significance of continued

investigation on innovative cancer management and raising general public awareness on

cancer problem and control. Improving the future of individuals diagnosed with

pancreatic cancer (PC) through the concerted efforts of policymakers, public health

professionals, clinicians and scientists, the Recalcitrant Cancer Research Act of 2012 lays

the foundation for a heightened focused on further development and use of prevention,

screening and therapeutic strategy (Rahib et al., 2014). Introduced initially as the

Pancreatic Cancer Research and Education Act, the Recalcitrant Cancer Research Act

was signed into law as part of the National Defense Authorization Act on January 2,

2013, through broad bi-partisan and bi-cameral support (The pancreatic cancer action

network, 2013). The genuine progress against PC as recalcitrant cancer warrants strategic direction and guidance on the continued understanding, development of efficient early detection strategy and identifying therapeutic targets that could stem the tide of its growing economic burden.

Continued research on the association between passive smoking exposure and the disease, as well as early shared exposure of these predictors, are critical to broadening the understanding of its significance to lifetime increased risk. The focus on obtaining a larger number of endpoints, it is paramount for future research to combine more cohorts to have a stronger and standardized sampling that yields a statistically significant assessment of predictors associated with pancreatic cancer. A synergy begets by outcomes research and epidemiology can provide unique and compelling insights on the significance of interventions designed to improve the quality and effectiveness of care in populations. It is important to acknowledge the need for continued research to establish a meaningful risk prediction models that could be practically applied in clinical settings to raise the accuracy of predicting the potential for PC. Given that surgical resection procedure is the only treatment approach that could improve survival rate, establishing a high-risk prediction model using novel early identification protocol of pre-malignant lesions and molecular profiling, as part of a personalized therapeutic approach and standardized methods of early detection, and prevention.

Pancreatic cancer (PC) involves both genetic and environmental factors, and like any other human diseases, PC is complex and multifactorial that has the greatest burden on society. According to Bookman et al. (2011), the development of high-density

genotyping platforms has allowed investigators to screen hundreds of thousands of genetic variants to test for associations with disease (p.2). Hindorff et al. (2011) asserted that to date, Genome Wide Association Studies (GWAS) have identified over 900 statistically significant findings in various diseases and conditions. While there is much work still needed to develop practical, ethical, useful policies on GWAS, it is imperative to embolden researchers in the continued exploration of genetic and environmental interactions associated with PC and CTSG-A that may identify additional risk factors or what proportion of cancer induction, promotion, expression is induced by inherited predisposition or combination of shared environmental, and biodemographic factors. Future research on the predictive value of whole-genome sequencing (WGS) in the healthy population is critical on the hypothesis of meaningful information that sheds light on individual differences in environmental sensitivity that will give summary information across a number of different loci may prove to be useful (Boardman et al., 2014; Lindor, Thibodeau, & Burke, 2017). The mechanism(s) through which environmental, genetic, biodemographic interaction (EGBI) with the particular focus on the effect of tobacco carcinogens as a shared environmental factor to shared genetic footprints in family cancer history (FCH) or its combined role remains unknown. Henceforth, it is critical to explore their correlation in future research, satisfying the sense of urgency for novel and innovative therapeutics. As stated by Lu et al. (2017), continued understanding of genomic variations in PC is crucial in providing an avenue for precision medicine. As emphasized by Lu et al. (2017), sustained understanding of genomic variations in PC is vital in providing an avenue for precision medicine. It is essential to highlight the

significance of these studies in providing fundamental knowledge for new and effective treatment strategies.

Conclusion

Pancreatic cancer has the global ranking of 13 as the most common cause of cancer and represents the 7th most frequent cause of cancer death, and accounts for about 3% of all cancers in the US with cancer mortality of 7% (American Cancer Society, Inc., 2016). These statistics justify the intent of this dissertation to determine whether there is existence or absence of correlation between tobacco use, gender, and age in the etiopathogenesis of PC and other cancer types with shared-gene association (CTSG-A), with the intent of advancing the existing body of knowledge on environmental, genetic and biodemographic interactions (EGBIs) in cancer evolution. While the results of this study supported the null hypotheses that smoking has no correlation with the prevalence of PC and CTSG-A, both gender and age are statistically significant predictors that supports the need for future research on the modification effect of shared environmental factors and etiopathogenic role of biodemographic factors (age, gender, race, socioeconomic status) in cancer evolution.

Ab-initio studies have established that family history of PC can manifest due to genetic factors and shared environmental factors. The scientific perspective of this dissertation, current, and past studies are parallel to Albert Einstein's concept of "natura naturans"—everything is connected. In this dissertation, the assumption that P16(CDKN2A), PRSS1, BRCA1, STK11, LKB1, bMLH1, and bMSH2 are correlated with the development of the disease is mathematically or statistically correct and deserves

further investigation. The results provided the rationale for further research on the pathopoiesis mechanism of shared environmental and genetic factors that are responsible for pancreatic cancer and other CTSG-A evolution. Such molecular window could initiate evidence-based discussions on the urgent need to revise or improve the BRFSS cancer survivorship module. While our understanding of the molecular events underlying multi-step carcinogenesis in PC has steadily increased (Lu et al., 2017), according to "Analysis of the President's FY 2018 Budget Request for Federal Research, Health, and Higher Education Programs" (2017), "the current administration's budget blueprint would reduce funding for Chronic Disease Prevention and Promotion at the CDC by about $164 million" (p. 27). For decades, the federal government has committed to the advancement of science and population health. It is not our duty to participate in a partisan debate, but rather protect our long history of closing the gap to equal access to quality health care through evidence-based studies. It is important to recognize the much-needed focus on policies that will promote broader population health, as well as potential public policies that could improve health behaviors easier, particularly for those who belong to vulnerable, high-risk groups. The assumption of the association of modifiable risk factors and CPG using the unified paradigm of cancer causation, or the probability of precise measurement of a risk factor that wakes up dormant mutated cancer genes using conceptual epidemiological quantum framework will be dependent upon access to cancer registry data.

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Appendix A

Genetic Alterations in Common Neoplasms of the Pancreas

TUMOR TYPE	GENE(S)	PREVALENCE OF THE ALTERATION	COMMENT
Acinar cell carcinoma	APC	15%	
	Acinar cell carcinoma	5%	
Invasive ductal Adenocarcinoma	KRAS	95%	KRAS mutations occur early, and KRAS mutations may be a target for early detection
	p16/CDKN2A	95%	
	TP53	75%	
	SMAD4	55%	SMAD4 loss associated with poor prognosis and widespread disease
	MLL3, TGFBR2, FBXW7, ARID1A, AIRID2, and ATM	<5%	Some of these, such as ATM, may be targetable therapeutically
IPMN	KRAS	80%	
	RNF43	75%	RNF43 is a marker of mucin-producing tumors because it is present in both IPMNs and MCNs
	GNAS	60%	GNAS is a marker of IPMNs. GNAS and/or KRAS mutations are present in >95% of all IPMNs
	p16/CDKN2A	Varies dependent on histologic grade	
	TP53	Varies dependent on histologic grade	Associated with higher grade lesions
	SMAD4	Varies dependent on histologic grade	Associated with higher grade lesions
	PIK3CA	10%	
MCN	KRAS	75%	

	RNF43	40%	RNF43 is a marker of mucin-producing tumors, present in IPMNs and MCNs
	p16/CDKN2A	Varies dependent on histologic grade	
	TP53	Varies dependent on histologic grade	Associated with higher grade lesions
	SMAD4	Varies dependent on histologic grade	Associated with higher grade lesions
Pancreatoblastoma	Imprinted region on chromosome 11	85%	Same region is targeted in hepatoblastoma and Wilms tumors
	CTNNB1 (beta-catenin)	55%	
	APC	10%	
PanNET	MEN1	45%	
	DAXX or ATRX	45%	Associated with ALT+
	TSC2, PTEN, and PIK3CA (mTOR pathway genes)	15%	Potentially targetable therapeutically with everolimus
SCN	VHL	50%	Among the cystic tumors of the pancreas, VHL loss is specific for SCN
SPN	CTNNB1 (beta-catenin)	95%	Immunolabeling for beta-catenin is useful diagnostically

ALT+ indicates an alternative lengthening of telomeres; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; PanNET, pancreatic neuroendocrine tumor; SCN, serous cystic neoplasm; SPN, solid-pseudopapillary neoplasm.

Note: Adapted from "Recent progress in pancreatic cancer" by Wolfgang et al., 2013, *CA: a cancer journal for clinicians, American Cancer Society,* 63(5), p. 327. Copyright 2013 American Cancer Society, Inc.

Appendix B

Cancer (CA) Types Surveyed During the 2014 BRFSS, Five-States Cancer Survivorship Module		Frequency	Percent	Valid Percent
Valid	Breast Cancer	1178	16.4	16.4
	Cervical Cancer	340	4.7	4.7
	Endometrial Cancer	178	2.5	2.5
	Ovarian Cancer	104	1.5	1.5
	Cancer of the Head and Neck	20	.3	.3
	Oral Cancer	22	.3	.3
	Pharyngeal Cancer	45	.6	.6
	Thyroid Cancer	131	1.8	1.8
	Cancer of the Larynx	5	.1	.1
	Colorectal Cancer	337	4.7	4.7
	Esophageal Cancer	13	.2	.2
	Liver Cancer	19	.3	.3
	Pancreatic Cancer	12	.2	.2
	Rectal Cancer	31	.4	.4
	Cancer of the Stomach	13	.2	.2
	Hodgkin's Lymphoma	61	.9	.9
	Leukemia	73	1.0	1.0
	Non-Hodgkin's Lymphoma	77	1.1	1.1
	Prostate Cancer	613	8.6	8.6
	Testicular Cancer	25	.3	.3
	Melanoma	964	13.4	13.4
	Other skin cancer	2183	30.5	30.5
	Lung Cancer	137	1.9	1.9
	Bladder Cancer	129	1.8	1.8
	Renal Cancer	100	1.4	1.4
	Cancer of the Bone	38	.5	.5
	Brain Cancer	16	.2	.2
	Neuroblastoma	5	.1	.1
	Other	300	4.2	4.2
	Total	7169	100.0	100.0

Appendix C

CA Type with SG-A Before Data Cleaning and Re-coding		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Other CA Types with 0-Known SG-A	1312	43.7	43.7	43.7
	Breast Cancer	473	15.8	15.8	59.4
	Endometrial Cancer	84	2.8	2.8	62.2
	Ovarian Cancer	40	1.3	1.3	63.6
	Cancer of the Head and Neck	8	.3	.3	63.8
	Colorectal Cancer	142	4.7	4.7	68.6
	Esophageal Cancer	6	.2	.2	68.8
	Pancreatic Cancer	6	.2	.2	69.0
	Cancer of the Stomach	5	.2	.2	69.1
	Leukemia	27	.9	.9	70.0
	Melanoma	460	15.3	15.3	85.3
	Lung Cancer	70	2.3	2.3	87.7
	Bladder Cancer	49	1.6	1.6	89.3
	Renal Cancer	45	1.5	1.5	90.8
	Brain Cancer	7	.2	.2	91.0
	Prostate Cancer	256	8.5	8.5	99.6
	Osteosarcoma (Bone)	13	.4	.4	100.0
	Total	3003	100.0	100.0	

Appendix D

Table D1.1

Prev1*Respondents Gender Crosstabulation

			Respondents Gender		Total
			Male	Female	
Prev1	BRCA1/STK11/LKB1/bML	Count	322	678	1000
	H1/bMSH2	Expected Count	409.2	590.8	1000.0
	P16(CDKN2A)/PRSS1	Count	370	321	691
		Expected Count	282.8	408.2	691.0
Total		Count	692	999	1691
		Expected Count	692.0	999.0	1691.0

Table D1.2

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	77.013[a]	1	.000		
Continuity Correction[b]	76.133	1	.000		
Likelihood Ratio	76.990	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	76.968	1	.000		
McNemar Test				.[c]	
N of Valid Cases	1691				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 282.77.

b. Computed only for a 2x2 table

c. Both variables must have identical values of categories.

Table D2.1

Prev1*Three Age Group Crosstabulation

Table 13A: Prev1 * Three Age Group Crosstabulation						
			Three Age Group			
			<51	52-69	70>	Total
Prev1	BRCA1/STK11/LKB1/bML H1/bMSH2	Count	62	369	569	1000
		Expected Count	74.5	389.7	535.8	1000.0
	P16(CDKN2A)/PRSS1	Count	64	290	337	691
		Expected Count	51.5	269.3	370.2	691.0
Total		Count	126	659	906	1691
		Expected Count	126.0	659.0	906.0	1691.0

Table D2.2

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	12.876[a]	2	.002
Likelihood Ratio	12.818	2	.002
Linear-by-Linear Association	12.869	1	.000
McNemar-Bowker Test	.	.	.[b]
N of Valid Cases	1691		

a. 0 cells (.0%) have expected count less than 5. The minimum

expected count is 51.49.

b. Computed only for a PxP table, where P must be greater than 1.

Table D3.1

Prev1*Four-Level Smoking Status Crosstabulation

			Four-Level Smoking Status				
			Now Smokes Everyday	Now Smokes Some Days	Former Smoker	Never Smoked	Total
Prev1	BRCA1/STK11/LKB1/bMLH1/bMSH2	Count	66	19	362	553	1000
		Expected Count	73.3	21.3	387.3	518.0	1000.0
	P16(CDKN2A)/PRSS1	Count	58	17	293	323	691
		Expected Count	50.7	14.7	267.7	358.0	691.0
Total		Count	124	36	655	876	1691
		Expected Count	124.0	36.0	655.0	876.0	1691.0

Table D3.2

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	12.228[a]	3	.007
Likelihood Ratio	12.229	3	.007
Linear-by-Linear Association	9.282	1	.002
McNemar-Bowker Test	.	.	.[b]
N of Valid Cases	1691		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 14.71.
b. Computed only for a PxP table, where P must be greater than 1.

Appendix E

Table E1.1

Prev2*Respondents Gender Crosstabulation

			Respondents Gender		
			Male	Female	Total
Prev2	P16(CDKN2A)/PRSS1/bM	Count	434	488	922
	LH1/bMSH2	Expected Count	377.3	544.7	922.0
	BRCA1/STK11/LKB1	Count	258	511	769
		Expected Count	314.7	454.3	769.0
Total		Count	692	999	1691
		Expected Count	692.0	999.0	1691.0

Table E1.2

Chi-Square Tests

	Value	df	Asymptotic Significance	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	31.709[a]	1	.000		
Continuity Correction[b]	31.152	1	.000		
Likelihood Ratio	31.926	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	31.690	1	.000		
McNemar Test				.c	
N of Valid Cases	1691				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 314.69.

b. Computed only for a 2x2 table

c. Both variables must have identical values of categories.

Table E2.1

Prev2*Three Age Group Crosstabulation

			Three Age Group			
			<51	52-69	70>	Total
Prev2	P16(CDKN2A)/PRSS1/ bMLH1/bMSH2	Count	82	366	474	922
		Expected Count	68.7	359.3	494.0	922.0
	BRCA1/STK11/LKB1	Count	44	293	432	769
		Expected Count	57.3	299.7	412.0	769.0
Total		Count	126	659	906	1691
		Expected Count	126.0	659.0	906.0	1691.0

Table E2.2

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	7.714[a]	2	.021
Likelihood Ratio	7.829	2	.020
Linear-by-Linear Association	6.644	1	.010
McNemar-Bowker Test	.	.	.[b]
N of Valid Cases	1691		

a. 0 cells (.0%) have expected count less than 5. The minimum
expected count is 57.30.

b. Computed only for a PxP table, where P must be greater than 1.

Table E3.1

Prev2*Four-Level Smoking Status Crosstabulation

			Four-Level Smoking Status				
			Now Smokes Everyday	Now Smokes Some Days	Former Smoker	Never Smoked	Total
Prev2	P16(CDKN 2A)/PRSS1 /bMLH1/b MSH2	Count	74	20	381	447	922
		Expected Count	67.6	19.6	357.1	477.6	922.0
	BRCA1/ST K11/LKB1	Count	50	16	274	429	769
		Expected Count	56.4	16.4	297.9	398.4	769.0
Total		Count	124	36	655	876	1691
		Expected Count	124.0	36.0	655.0	876.0	1691.0

Table E3.2

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	9.171[a]	3	.027
Likelihood Ratio	9.186	3	.027
Linear-by-Linear Association	6.434	1	.011
McNemar-Bowker Test	.	.	.[b]
N of Valid Cases	1691		

a. 0 cells (.0%) have expected count less than 5. The minimum
expected count is 16.37.

b. Computed only for a PxP table, where P must be greater than 1.