The Contribution of Modifiable and Non-Modifiable Risk Factors for Pancreatic Cancer: A Geospatial Analysis and Literature Review

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Abstract

Pancreatic cancer is an important public health issue, due to its silent nature, high mortality rates, and low overall survival rates. Pancreatic cancer is the eleventh most diagnosed cancer in the United States, representing about 3.2% of all new cancer cases in the United States. However, pancreatic cancer is disproportionately deadly, ranking as the fourth most common cause of cancer death in both men and women in the United States. The risk of developing pancreatic cancer is related to various modifiable and non-modifiable risk factors. This review summarizes literature on the associations between the risk of pancreatic cancer and various modifiable and non-modifiable risk factors. Thirteen articles were retrieved for the evaluation of the effects of modifiable and non-modifiable risk factors on the risk of developing pancreatic cancer. Data on smoking, diabetes, and obesity were correlated with age-adjusted pancreatic cancer incidence rates by county for Pennsylvania and by Allegheny County zip code through EDDIE and the Environmental Public Health Track network. The literature review found that non-modifiable risk factors, such as BRCA mutations, blood type, pancreatitis, and mutations in tumor suppressor and cell proliferation genes to be associated with a higher risk of developing pancreatic cancer. Modifiable risk factors, such as smoking, alcohol intake, diabetes, and obesity, were also found to be associated with increased risk of pancreatic cancer. Across counties in Pennsylvania, risk factors such as diabetes, obesity, and smoking were shown to have very weak, negative associations with risk of pancreatic cancer age-adjusted incidence rates. However, when examining age-adjusted, 10-year, pancreatic cancer incidence rates by Allegheny County zip codes, modelled rates of obesity and smoking by zip code were shown to have moderate, positive correlations with rates of pancreatic cancer. The correlation between smoking and age-adjusted

incidence rates of pancreatic cancer, and obesity and age-adjusted incidence rates of pancreatic cancer within zip codes of Allegheny County was 0.247 and 0.29, respectively. Through a better understanding of risk factors for pancreatic cancer, we can help reduce the risk of negative health outcomes for a disease with a high mortality rate and significant public health significance.

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Preface

I want to thank all of the faculty and staff at the University of Pittsburgh, Graduate School of Public Health for their contributions towards this review. In addition, I want to thank Kristin Selker, Jamie Sokol, and Max Slater at the Allegheny County Health Department for providing me with the zip code level pancreatic cancer data. Below is the disclaimer from the Allegheny County Health Department:

"These data were compiled by the Allegheny County Health Department and supplied by the Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Allegheny County Health Department and Pennsylvania Department of Health specifically disclaim responsibility for any analyses, interpretations or conclusions."

1.0 Introduction

Pancreatic cancer is the eleventh most diagnosed cancer in the United States, representing about 3.2% of all new cancer cases in the United States. Despite being classified as a rare type of cancer, pancreatic cancer accounts for nearly eight percent of all cancer deaths in the United States. The American Cancer Society's case count estimates for pancreatic cancer in the United States for 2020 are about 57,600 people (30,400 men and 27,200 women). Pancreatic cancer has a poor prognosis with short survival time, ranking as the fourth most common cause of cancer death in both men and women in the United States. This relatively high death rate is because cancer of the pancreas is often silent and is usually diagnosed at an advanced stage. According to the American Cancer Society, the 5-year relative survival rate of pancreatic cancer for localized pancreatic cancer, meaning there is no spread of the cancer outside of the pancreas, is 37 percent. The 5-year relative survival rate of pancreatic cancer goes down as the cancer begins to spread to other parts of the body. If the pancreatic cancer is regional, meaning it has spread to nearby structures or lymph nodes, then the 5-year relative survival rate drops to 12 percent. If the pancreatic cancer becomes distant, meaning it has spread to other organ systems of the body, then the 5-year relative survival rate drops to 3 percent. Most cases of pancreatic cancer are diagnosed when the cancer has become distant because pancreatic cancer usually shows little or no symptoms until it is in the later stages of its disease progression. Pancreatic cancer is an important topic in public health because of the cancer's high mortality rate, its silent nature, and its increasingly low 5-year relative survival rate as the disease progresses.

There are many different forms of pancreatic tumors. Pancreatic tumors are classified according to their cell type of origin, structure, and behavior (Hassan, et al., 2007). The pancreas is a multifunctional organ consisting of a variety of cell types (Bastidas, 2000). The exocrine portion of the pancreas is comprised of duct cells and acinar cells that produce a combination of gastric enzymes needed for digestion (Hollingsworth, 1999). In contrast, the endocrine portion of the pancreas contains β cells and other types of endocrine cells that produce hormones, including insulin, that are dispersed throughout the body and that are required for glucose metabolism (Cotran, 1999). Most exocrine pancreatic cancers are adenocarcinomas. These tumors originate in the epithelial cells lining the pancreatic duct, form gland-like structures, and account for 90% of all pancreatic cancers (Fesinmeyer et al. 2005). Mucinous tumors, another type of exocrine pancreatic cancer, is the second most common histologic type of pancreatic cancer, accounting for <10% of all tumors. Cancers of the endocrine pancreas are less common, occurring at a rate of about five per million person-years, and accounting for <5% of all pancreatic cancers (Mullan, 2001). These tumors arise from pancreatic islet cells, including β cells and α cells (Cotran, 1999).

Risk factors for pancreatic cancer can be split into two categories: non-modifiable or modifiable. Non-modifiable risk factors are risk factors that cannot be changed or modified through lifestyle or behavior. These risk factors are inherited or genetic. Non-modifiable risk factors for pancreatic cancer include familial history and genetic markers for pancreatic cancer, age, hereditary and other forms of chronic pancreatitis, and non-O blood group (Maisonneuve & Lowenfels, 2015). Modifiable risk factors are risk factors that can be changed or modified through lifestyle or behavior. Modifiable risk factors can be defined as environmental or behavioral risk

factors, in that one's environment and behavior can increase or decrease the likelihood of developing pancreatic cancer. Modifiable risk factors for pancreatic cancer include smoking, obesity, diabetes, dietary factors such as non-vegetarian diet, and toxins (Maisonneuve & Lowenfels, 2015). Smoking, obesity, and dietary factors are modifiable risk factors that are dependent on one's behavior, while exposure to toxins can be attributed to one's environment, such as workplace or occupation.

Pennsylvania has the fourth highest age-adjusted incidence rate of pancreatic cancer of all the states in the United States, behind the District of Columbia, New Jersey, and Mississippi. According to data collected through the Center for Diseases Control and Prevention (CDC) and the National Cancer Institute (NCI), the age-adjusted incidence rate of pancreatic cancer in Pennsylvania from 2013 through 2017 was 14.3 cases per 100,000 persons. The age-adjusted incidence rate of pancreatic cancer in the United States was 13.1 per 100,000 men and women per year from 2013 to 2017.

Pancreatic cancer is an important public health due to its silent nature and high mortality rate. This review will examine the existing literature on modifiable and non-modifiable risk factors for pancreatic cancer. We will also examine age-adjusted pancreatic cancer incidence rates for zip codes within Allegheny County (AC) and their association with age-adjusted, modelled obesity and smoking rates by zip code for the 97 Zip codes within AC from 2008 to 2017.

2.0 Methods

2.1 Literature Review

Several procedures were followed to create a high-quality, comprehensive review of the existing literature on pancreatic cancer. First, a comprehensive review of peer-reviewed articles based on a wide range of search terms from multiple databases: PubMed, Medline, and Google Scholar. All searches were limited from January 1990 to October 2020. Because the researchers can only read and interpret literature in English, the search was restricted to this language. If the paper could not be translated to English, then it was excluded. In addition, the research was restricted to studies that were based in the United States, with exception to some studies that were multinational cohort studies but included cohorts from the United States.

Search terms for these articles included “pancreatic cancer”, “epidemiology of pancreatic cancer”, “pancreatic cancer incidence”, and “pancreatic cancer prevalence”. This was done to collect a broad range of articles pertaining to pancreatic cancer to serve as starting point for the review. Second, a review of the references for each of the peer-reviewed articles was conducted in order to find additional articles or to corroborate the researched article. This was done to narrow the amount of studies and articles that could be used in the review. Third, a search of articles relating to specific risk factors, modifiable and non-modifiable, was conducted using the previously searched articles identified from the prior two reviews. Search terms for peer-reviewed articles about modifiable risk factors included “pancreatic cancer smoking”, “pancreatic cancer alcohol”, “pancreatic cancer nutrition”, “pancreatic cancer diet”, “pancreatic cancer obesity”,

"pancreatic cancer pancreatitis", and "pancreatic cancer diabetes". Search terms for peer-reviewed articles about non-modifiable risk factors included "pancreatic cancer familial history", "pancreatic cancer p53", "pancreatic cancer BRCA", "pancreatic cancer blood type", "pancreatic cancer genetic mutations", "pancreatic cancer CDKN2A", "pancreatic cancer SMAD4", "pancreatic cancer KRAS", and "pancreatic cancer familial pancreatitis".

For the risk factors smoking, blood type, diabetes, alcohol intake, obesity, and BRCA1/BRCA2 mutations, we calculated the population attributable fraction (PAF) which is the fraction of pancreatic cancers (PCs) attributable to exposure. PAF is the estimated fraction of all cases that would not have occurred if there had been no exposure. The equation used to calculate PAFs was $PAF = Pe(RRe-1) /[1 + Pe(RRe-1)]$. RR_e is defined as relative risk for those exposed to the risk factor. These values were obtained from the studies in the literature review. P_e is defined as the general population exposed to a risk factor. These percentages were obtained through the WHO Global Health Risk report (Mathers et al. 2009).

2.2 Pennsylvania County Analysis

Data for the county level age-adjusted incidence rates of pancreatic cancer from 2013 to 2017 was obtained through the Pennsylvania Enterprise Data and Dissemination Informatics Exchange (EDDIE). Age-adjusted rates are rates that would have existed if the population under study had the same age distribution as the "standard" population. Therefore, they are summary measures adjusted for differences in age distributions. Data for smoking, obesity, and diabetes rates by county in Pennsylvania between 2017 and 2019 were obtained from the Pennsylvania

Department of Health Pennsylvania Health Statistics. Smoking, obesity, and diabetes rates are reported as percentages. Percent smoking was measured by the number of people who are listed as current smokers. Percent smoking does not include those who are attempting to quit. Percent obesity was measured by the number of people that had a BMI greater than or equal to 30 and have an official diagnosis of obesity. Percent diabetes was measured by the number of people ever told they had diabetes. Official diagnosis or the measurement of blood sugar levels was not mentioned as part of the measurement.

2.3 Allegheny County Zip Code Analysis

Data for pancreatic cancer risk factors smoking and obesity by county in Pennsylvania came from two sources. Zip code level smoking and obesity data for Allegheny County were obtained from data conducted in the Environmental Public Health Tracking network (Hinojosa et al., 2014). Zip code level incidence data from 97 zip codes within Allegheny County were obtained from the Allegheny County Health Department (ACHD). Age-adjusted incidence rates of pancreatic cancer, for the period 2008-2017 were obtained for each of these ZIP codes and entered into a database. Zip codes within Allegheny County with less than 10 pancreatic cancer cases counts over the 10-year time interval were excluded from analysis. SPSS 26.0 was used to conduct the overall multiple linear regression of the two independent variables effects on pancreatic cancer rates as well. The Pearson correlation evaluated the linear relationship between two continuous variables, which in the study was between age-adjusted incidence rates of pancreatic cancer and smoking rates and between age-adjusted incidence rates of pancreatic cancer and obesity rates in Allegheny County, Pennsylvania. The Spearman rank correlation was used to measure the degree

of association between two variables. The Spearman rank correlation test does not carry any assumptions about the distribution of the data. The one-way analysis of variance (ANOVA) is used to determine whether there are any statistically significant differences between the means of age-adjusted incidence rates of pancreatic cancer, smoking rates, and obesity rates by zip code in Allegheny County, Pennsylvania. The ANOVA test was used to determine whether any of the mean rates for age-adjusted pancreatic cancer, smoking, and obesity were statistically significantly different from each other.

ArcMap 10.7.1 was used to create the maps in the review. Data for each risk factor mapped across zip codes within Allegheny County was obtained from Hinojosa et al (2014). Data for age-adjusted incidence rates of pancreatic cancer across Allegheny County was obtained from the ACHD. Zip codes that were excluded from the maps were zip codes that did not have the required number of pancreatic cancer case counts within the given time interval. In addition, zip codes with no data for smoking and obesity were also excluded. These excluded zip codes were presented on the maps as white. For zip codes used in the maps that met inclusion criteria, a green to blue gradient was used in each of the generated maps.

3.0 Results

3.1 Literature Review

When using the search databases such as PubMed, Medline, and Google Scholar, the search yielded a large number of studies that pertained to pancreatic cancer and its risk factors. However, all of the over 140,000 articles that were identified in the initial search could not be used. Duplicates from the initial review of peer-reviewed articles were excluded. In many cases, the webpages where the articles were to be found were not available or removed and therefore excluded. In addition, any articles that were not available to the public (free use) were excluded from the review. This narrowed the number of articles available for the review down to 94 articles. A list of exclusion criteria to facilitate article screening was used to help determine which of the 94 articles should be included in the review. This exclusion criteria included the following: full text not available, studies based outside the United States, studies were reviews or meta-analyses, studies that did not adjust for at least one confounder (age, smoking, BMI, etc), studies unavailable in English, French, or Spanish (or could not be translated to English), articles published before 1990, and non-observational studies. After the review and screening process, 13 articles were used for this review.

Literature review search strategy and selection criteria of MEDLINE/PubMED/Google Scholar articles (January 1990 – October 2020) on the relationship between pancreatic cancer and non-modifiable and modifiable risk factors

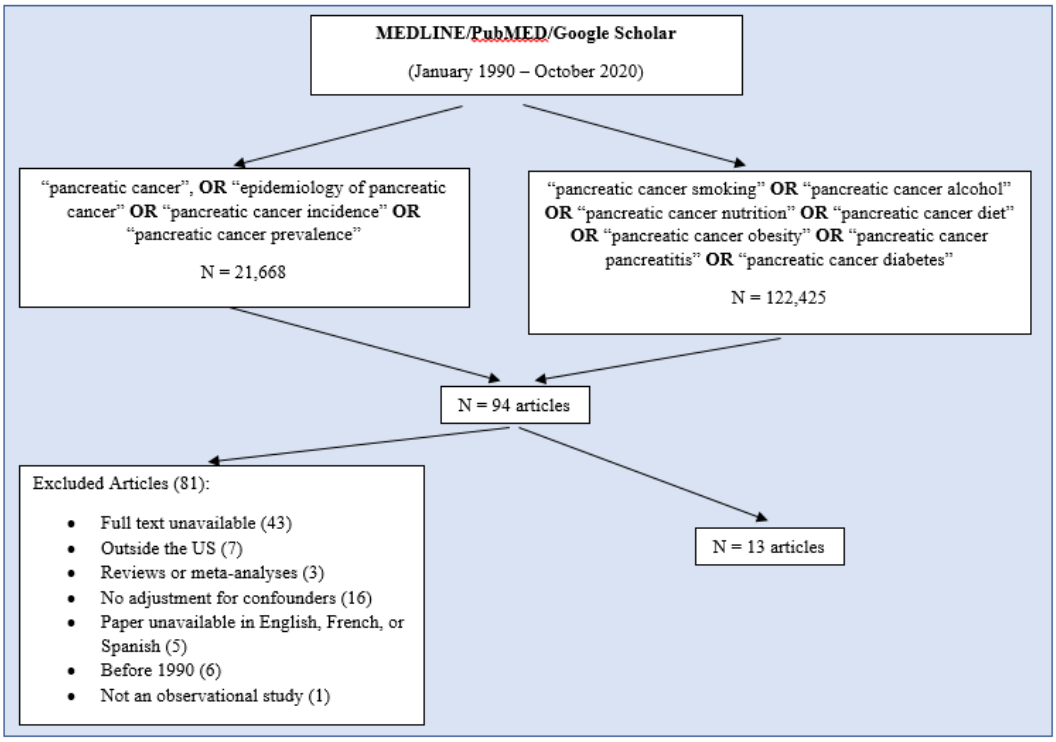
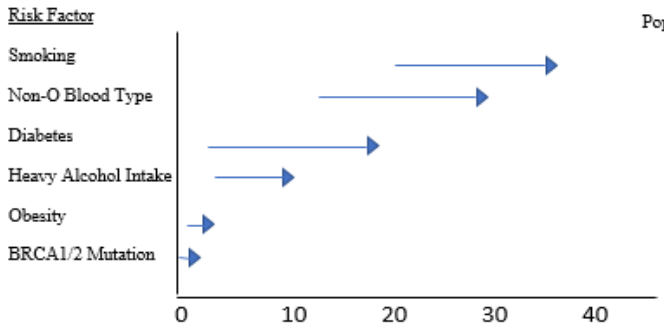


Figure 1 Literature Review Search Strategy

Figure 2 ranks the population attributable fraction for individual exposure variables, obtained by combining estimates of the proportion of the population exposed and of the relative risk for each exposure variable. Population attributable fraction for a population is the proportion of incidents in the population that are attributable to the risk factor. The range of the population exposed that was used is for the United States. The estimated for the population exposed by risk factor was obtained through the *WHO Global Health Risks* report. Relative risks were based on the measures obtained from each study in this review.



Risk Factor	Population Exposed	RR	Attributable Fraction (%)
Smoking	25-40%	2.1-2.4	21-36
Non-O Blood Type	50-60%	1.3-1.7	13-29
Diabetes	4-17%	1.5-2.0	2-15%
Heavy Alcohol Intake	5-20%	1.5-1.6	2.4-10.7
Obesity	20-40%	1.03-1.05	0.5-1.9
BRCA1/2 Mutation	0.02-0.04%	2.26-3.51	0-1%

Figure 2 Population Attributable Fraction

In Figure 2, we estimate that 21–36% of all pancreatic cancer (PC) might be attributable to tobacco smoking. Another important risk factor is blood group where we estimate the proportion of PC attributable to be 13% to 29%. For diabetes, we estimated that the proportion of PC attributable to diabetes could range from 2% to 15%. For heavy alcohol intake, we estimate the proportion of PC attributable to alcohol intake to be 2.4% to 10.7%. For obesity, we estimate the proportion of PC attributable to obesity to be 0.5% to 1.9%. For BRCA1/BRCA2 mutations, we estimate the proportion of PC attributable to BRCA1/BRCA2 mutations to be less than 1%.

3.2 Non-Modifiable Risk Factors

3.2.1 BRCA1/BRCA2 Mutations

The BRCA1 gene is tumor suppressor gene and is responsible for repairing damaged DNA. The BRCA2 gene acts as a mediator in the cellular reproduction process (Roy, Chun & Powell, 2011). Iqbal et al. found that of the 5089 women BRCA1 and BRCA2 mutation carriers, they saw

a statistically significant 2.4-fold increase in the incidence of pancreatic cancer in female BRCA mutation carriers (P = 0.03). The increase in the incidence of pancreatic cancer was similar for BRCA1 mutation carriers (SIR = 2.55) and BRCA2 mutation carriers (SIR = 2.13) (Iqbal et al., 2012).

A familial history of BRCA1 and BRCA2 mutations has been shown in the literature to be a potential risk factor for pancreatic cancer. In a study by Petersen et al. that examined over 476 patients with pancreatic cancer (2006), researchers found that familial pancreatic cancer (FPC) is an identifiable entity (kindreds containing at least two affected first-degree relatives). Supporting literature found that genetic predisposition is a plausible explanatory etiology (Hruban 1998, Lynch 1996). This conclusion was reached after Petersen et al. adjusted their analyses of FPCs for age. In addition, a study by Lal G, et al. reported that 13% of families classified as at high or intermediate familial risk of pancreatic cancer were found to carry *BRCA1*, *BRCA2*, or *p16* germ line mutations (Lal 2000). Mutations in the BRCA1 and BRCA2 genes have also been shown to influence the survival rate of those diagnosed with pancreatic cancer. Iqbal et al. reported a poor overall survival in both men and women with a BRCA1 mutation or a BRCA2 mutation, compared to men and women without a BRCA1 or BRCA2 mutation. The average time from diagnosis to death was 1 year for both groups and the 5-year survival was 5% for BRCA1 carriers and 4% for BRCA2 carriers. (Iqbal et al., 2011). The survival time for patients with BRCA1/BRCA2 was lower compared to the American Cancer Society's survival time for pancreatic cancer.

3.2.2 Blood Type

Non-O blood type has been shown to be associated with an increased risk of pancreatic cancer. According to a study by Wolpin et al. of 107,553 people (2009), blood types A, B, and AB were associated with the risk of developing pancreatic cancer (P = .004; log-rank test). Compared with participants with blood group O, those with blood groups A, AB, or B were more likely to develop pancreatic cancer (adjusted hazard ratios for incident pancreatic cancer were 1.32 (95% confidence interval {CI} = 1.02, 1.72), 1.51 (95% CI = 1.02 to 2.23), and 1.72 (95% CI = 1.25 to 2.38), respectively. Overall, 17% of the pancreatic cancer cases were attributable to inheriting a non-O blood group (blood group A, B, or AB). These analyses controlled for age, smoking, body mass index, physical activity, and diabetes.

3.2.3 Somatic Mutations: p53/CDKN2A/SMAD4/KRAS genes

These are somatic mutations, not germ line mutations. These somatic mutations occur in the cell malignant transformation, and as prognostic biomarker and/or treatment selection markers, but not risk susceptibility markers. Somatic mutations are acquired, as opposed to germ line mutations which are passed on from parent to child. Multiple studies have shown how somatic mutations in tumor suppressor and cell proliferation genes increase the risk of pancreatic cancer. In a study by Hwang, Gordon, Anderson, & Parekh, they found the p53 gene, or TP53, was one of the most frequently mutated genes in all cancers and is mutated in 70% of pancreatic cancers (1998). TP53 is the tumor suppressor, which transcriptionally activates target genes in response to cellular stress such as oxidative stress or DNA damage and thus induces growth arrest or apoptosis

(Levy, 1998). It also increases cyclin-dependent kinase inhibitor CDKN1A expression, thus stopping cell cycle progression (Bates, 1998).

A study by McWilliams et al. of 1537 participants from October 2000 to January 2011 found that *CDKN2A* mutation carriers were more likely to have a family history of pancreatic cancer (P=0.003) (2011). In their analyses, McWilliams et al. adjusted for smoking status, and familial history of cancer. In addition, McWilliams et al. observed that among cases who reported having a first-degree relative with pancreatic cancer, the carrier proportions were 3.3% (2011). CDKN2A (also known as p16-INK4a, MTS-1, or CDK4I) is the tumor suppressor, which regulates cell cycle progression by inhibiting cyclinD-CDK4 and cyclinD-CDK6 complexes responsible for initiating the G1/S phase transition (Cicenas et al., 2017).

A study by Ahmed et al. examining the effects of SMAD4 mutations, they found that SMAD4 mutations are relatively specific and its inactivation is found in more than 50% of invasive pancreatic adenocarcinomas (2017). Additionally, a study by Blackford et al. that examined 89 pancreaticoduodenctomy patients found that when adjusted for age, lymph node status, margin status, and tumor size, SMAD4 gene inactivation was significantly associated with shorter overall survival (hazard ratio, 1.92; 95% CI, 1.20-3.05; p = 0.006). Patients with SMAD4 gene inactivation survived a median of 11.5 months, compared with 14.2 months for patients without SMAD4 inactivation (2009). SMAD4 (also known as DPC4 or MADH4) is tumor suppressor protein, which translocates to the nucleus as heterotrimeric SMAD2/SMAD3-SMAD4 complex after TGF family receptors activation, where it activates the expression of genes and causes growth inhibition (Cicenas et al., 2017).

A study by Bournet et al. of 219 patients diagnosed with pancreatic cancer (2016) found that 147 harbored a codon-12 *KRAS* mutation (G12D: 73; G12V: 53; G12R: 21) and 72 had a wild-type *KRAS*. In their analyses, researchers adjusted for age, progression of pancreatic cancer, and CA 19-9 levels. Bournet et al. observed no difference in the overall survival between patients with a mutant *KRAS* (8 months; 95% confidence interval (95% CI): 8.7–12.3) and the wild-type (9 months; 95% CI: 8.7–12.8; hazard ratio (HR): 1.03; *P*=0.82) (2016). However, Bournet et al. found that patients with a G12D mutation had a significantly shorter OS (6 months; 95% CI: 6.4–9.7) compared with the other patients (OS: 9 months; 95% CI: 10–13; HR: 1.47; *P*=0.003) KRAS (also known as K-Ras 2, Ki-Ras, c-K-ras, or c-Ki-ras) is a small GTPase (21 kDa), which binds guanosine triphosphate and diphosphate nucleotides (Cicenas et al., 2017). The KRAS gene helps with cell proliferation and repair.

3.2.4 Pancreatitis

In a cohort study by Lowenfels, Maisonneuve, DiMagno, et al. that examined 246 patients with pancreatitis from 10 different counties in 1996 (1997), they found that The cumulative risk of pancreatic cancer in these patients to age 70 years was 40% (95% CI = 9%–71%). The patients in the study were chronic and acute forms of pancreatitis. In addition, they found that for the subgroup of 105 patients with a paternal parent of origin, the cumulative risk of cancer to age 70 years was approximately 75% (95% CI = 32%–100%). A family history for the parental source of pancreatitis was available for 168 (71%) of the 238 patients in this cohort who remained free of cancer: 99 patients had a father or paternal relative with pancreatitis compared with 69 who had a

mother or maternal relative with pancreatitis (P = .024) (Lowenfels AB, Maisonneuve P, DiMagno EP, et al., 1997). In these analyses, Lowenfels, Maisonneuve, DiMagno, et al. adjusted for age, sex, and country. A family history of the parental-source pancreatitis was known for six of the eight patients with hereditary pancreatitis in the cohort who eventually developed pancreatic cancer: in all six patients, the paternal family had pancreatitis. Hereditary pancreatitis is characterized by recurrent attacks of abdominal pain beginning early in life and affects several family members in different generations. The inheritance pattern is believed to be autosomal dominant, with an estimated penetrance of 80% (Sibert, 1978).

3.3 Modifiable Risk Factors

3.3.1 Smoking

Multiple studies showed that smoking increased the risk of pancreatic cancer or increased the number of genetic mutations. In a study by Lynch et al. that pooled more than 1,481 cases and 1,539 controls from the international Pancreatic Cancer Cohort Consortium nested case-control study, they found that when compared with never smokers, current smokers had a statistically significant elevated risk of pancreatic cancer with an odds ratio (OR) = 1.77, 95% confidence interval (CI): 1.38, 2.26; (2009). Additionally, they discovered that the risk of pancreatic cancer increased significantly with greater intensity of smoking (30 cigarettes/day: OR = 1.75, 95% CI: 1.27, 2.42) compared to non-smokers. Lynch et al. found that, compared to not smoking, duration

of smoking increased the risk of pancreatic cancer (50 years: OR = 2.13, 95% CI: 1.25, 3.62). In addition, Lynch et al. found that an increased cumulative smoking dose increased the risk for pancreatic cancer in those who smoked (40 pack-years: OR = 1.78, 95% CI: 1.35, 2.34) compared to non-smokers. In these analyses, Lynch et al. adjusted for sex, age, body mass index, and diabetes.

In a study by Blackford et al. that examined 114 pancreatic adenocarcinomas in 2008 (2009), Blackford et al. found that, when adjusted for age and gender, multivariate Cox proportional models revealed significantly more non-synonymous mutations in the carcinomas obtained from ever smokers (mean, 53.1 mutations per tumor; SD, 27.9) than in the carcinomas obtained from never smokers (mean, 38.5; SD, 11.1; P = 0.04). The difference between smokers and nonsmokers was not driven by mutations in known driver genes in pancreatic cancer (KRAS, TP53, CDKN2A/p16, and SMAD4), but instead was predominantly observed in genes mutated at lower frequency. However, they did conclude that pancreatic carcinomas from cigarette smokers harbor more mutations than do carcinomas from never smokers.

3.3.2 Alcohol Intake

Increasing levels of alcohol intake was found to be associated with an increased risk of pancreatic cancer. In a study by Jiao et al. that studied 470,681 participants ages 50-71 from 1995 to 1996 (2009), researchers found that, after adjusting for smoking, those who consumed 6 or more drinks per day, compared with light drinkers, had a relative risk of 1.55 (95% CI: 1.13, 2.13; p =

0.004) and 3 or more drinks per day had a relative risk of 1.45 (95% CI: 1.17, 1.80; p = 0.002). Jiao et al. also found that, compared with light drinkers of liquor, heavy drinkers of liquor had a 62% increased risk of developing pancreatic cancer (95% CI: 1.24, 2.10; p = 0.001). The elevated relative risk for heavy liquor use was statistically significant in men but not in women. However, beer or wine use was not associated with the risk.

3.3.3 Diet

Dietary flavenol intake has been shown to be associated with risk of pancreatic cancer. In a cohort study by Nöthlings et al. that examined more than 215,000 men and women aged 45-75 year from 1993 to 1996 (2007), they found, after adjusting for smoking, age, and history of diabetes, that the intake of total flavonols was associated with a reduced pancreatic cancer risk (relative risk for the highest vs. lowest quintile = 0.77, 95% confidence interval: 0.58, 1.03; p = 0.046). Of the three individual flavonols, kaempferol was associated with the largest risk reduction (relative risk = 0.78, 95% confidence interval: 0.58, 1.05; p = 0.017) .Intake of processed meat and red meat, to a lesser extent, was inversely associated with flavonol intake. They concluded that intake of flavonols was associated with a reduced pancreatic cancer risk, specifically Kaempferol, as it showed slightly stronger inverse associations than quercetin or myricetin.

3.3.4 Diabetes

In a comparative study by Pannala et al. that examined 512 newly diagnoses pancreatic cancer cases and 933 controls of similar age (2008), they found that, after adjusting for age and sex, that the overall prevalence of diabetes (DM) (reported treatment for DM and/or FBG level ≥126 mg/dL) was higher in cases compared with controls (47.4% vs 7.2%; $P < .001$). Overall, only 14% of patients with pancreatic cancer had normal FBG levels as compared with 59% of controls ($P < .001$). Patients were classified as diabetic if they had an fasting blood glucose (FBG) level ≥126 mg/dL or reported being on antidiabetic treatment; 213 of 512 pancreatic cancer cases (41.6%) had an FBG level ≥126 mg/dL as compared with 53 of 933 controls (5.7%) ($P < .001$). Pannala et al. also reported that in univariate pancreatic cancer cases were 5 times more likely to have impaired fasting glucose (IFG) (95% CI; 3.4–6.0) and 26 times more likely to be diabetic compared with controls (95% CI; 17.6–37.1). In multivariate analyses, diabetes was 14 times more likely in patients with pancreatic cancer as compared with controls (95% confidence interval, 8.7–21.5), after controlling for age, sex, BMI, family history of DM, smoking history, and weight loss of 2.3 kg (5 lb.) or greater. Patients were classified as having DM if the FBG level was ≥126 mg/dL (7 mmol/L), as having impaired fasting glucose (IFG) if their FBG value was between 100 and 125 mg/dL (5.6–6.9 mmol/L), and as having normal fasting glucose (NFG) if their FBG value was ≤99 mg/dL (5.5 mmol/L).

3.3.5 Obesity

Obesity was shown to have an association with risk of pancreatic cancer. In a study by Michaud et al. that examined 46,648 men and 117,041 women (2001), men and women with a BMI of 30 or higher had a 72% increase in the risk of pancreatic cancer compared with men and women with a BMI of less than 23, after adjusting for age and smoking. In multivariable analyses, an increment of 1 BMI unit (1 kg/m^2) was associated with a 5% increased risk of pancreatic cancer in the HPFS (RR, 1.05; 95% CI, 1.00-1.11) and a 3% increased risk in the NHS (RR, 1.03; 95% CI, 1.00-1.07).

3.4 Data Analysis

3.4.1 Pennsylvania County Analysis

Across all the counties in Pennsylvania, the age-adjusted incidence rates for pancreatic cancer ranged from 9.8 cases per 100,000 persons to nearly 20.0 cases per 100,000 from 2013 through 2017. Clarion County had the highest reported county age-adjusted incidence rate with about 19.8 cases per 100,000 from 2013 through 2017 while Indiana County had the lowest reported county age-adjusted incidence rate of 9.8 cases per 100,000 persons from 2013 through 2017 (Table 1).

Table 1 Age-Adjusted Incidence Rates of PC, Smoking Rates, Obesity Rates, and Viabetes rates by County, Pennsylvania

County	Age-Adjusted PC rate per 100,000	Current Smoker (%)	Obesity (%)	Told They Ever Had Diabetes (%)
Adams	15.5	17	32	13
Allegheny	15.1	18	30	10
Armstrong	13.9	21	39	15
Beaver	16.4	21	34	8
Bedford	14.3	19	34	11
Berks	13.3	17	34	9
Blair	15	19	34	11
Bradford	17.1	21	36	12
Bucks	14.7	13	28	13
Butler	13.9	21	34	8
Cambria	13.7	21	39	15
Carbon	17.5	18	32	12
Centre	13	15	34	10
Chester	12.5	11	22	7
Clarion	19.4	27	41	14
Clearfield	12	27	41	14
Clinton	12.2	21	36	12
Columbia	17.6	15	34	10
Crawford	14	26	35	12
Cumberland	13.3	18	30	12
Dauphin	13.7	20	32	10
Delaware	15	12	26	9
Elk	13	27	41	14
Erie	14.4	20	29	9
Fayette	12.8	20	39	13
Franklin	12.4	17	32	13
Greene	12.4	20	39	13
Huntingdon	11.8	19	34	11
Indiana	9.8	21	39	15
Jefferson	12.2	27	41	14
Juniata	14	19	34	11
Lackawanna	13.9	24	29	11
Lancaster	13.3	13	34	13
Lawrence	18.4	26	35	12
Lebanon	14.3	20	32	10
Lehigh	14.8	18	32	12
Luzerne	13.8	24	29	11

Lycoming	12.8	21	36	12
McKean	13.1	27	41	14
Mercer	10.3	26	35	12
Mifflin	12	19	34	11
Monroe	16.3	19	35	12
Montgomery	14	10	29	9
Montour	14.7	15	34	10
Northampton	14.8	18	32	12
Northumberland	14	15	34	10
Perry	11.1	18	30	12
Philadelphia	15.1	21	34	12
Pike	11	19	35	12
Schuylkill	17.4	17	34	9
Snyder	10.8	15	34	10
Somerset	15.2	21	39	15
Susquehanna	13.9	19	35	12
Tioga	15.8	21	36	12
Union	15.7	15	34	10
Venango	12.1	26	35	12
Warren	13.3	27	41	14
Washington	12.5	20	39	13
Wayne	13.7	19	35	12
Westmoreland	15	20	32	11
Wyoming	15.6	24	29	11
York	14.7	16	30	9

*Data for age-adjusted incidence rates came from EDDIE, 2013-2017; per 100,000; rate for all ages

**Data for Current Smoker, Obesity, and Diabetes came from the Pennsylvania Department of Health. Health Statistics, 2017-2019

*** Age-adjusted rates of Pancreatic Cancer were measured per 100,000

**** The counties of Cameron, Forest, Fulton, Potter and Sullivan were excluded from analysis due to having a low case count over the

Seven counties in Pennsylvania displayed statistically significantly higher or lower age-adjusted rates of pancreatic cancer compared to the other counties in Pennsylvania. From 2013 through 2017, the counties of Clarion, Lawrence, Allegheny, and Schuylkill displayed statistically significantly higher age-adjusted rates of pancreatic cancer, compared to other counties across

Pennsylvania. In the same time frame, the counties of Chester, Indiana, and Mercer displayed statistically significantly lower age-adjusted rates of pancreatic cancer. Of the four counties that had statistically significant, higher age-adjusted rates of pancreatic cancer, three counties (Clarion, Indiana, and Mercer) were in southwestern Pennsylvania.

Age-adjusted incidence rates of pancreatic cancer per 100,000 from counties across Pennsylvania were correlated with their respective rates of smoking, obesity, and prevalence of diabetes. The results show that each of the associations had a very weak, negative correlation. Age-adjusted incidence rates of pancreatic cancer and smoking had a correlation of -0.045 with a p-value of 0.00 (Figure 3). The R^2 value for Figure 3 was 0.002.

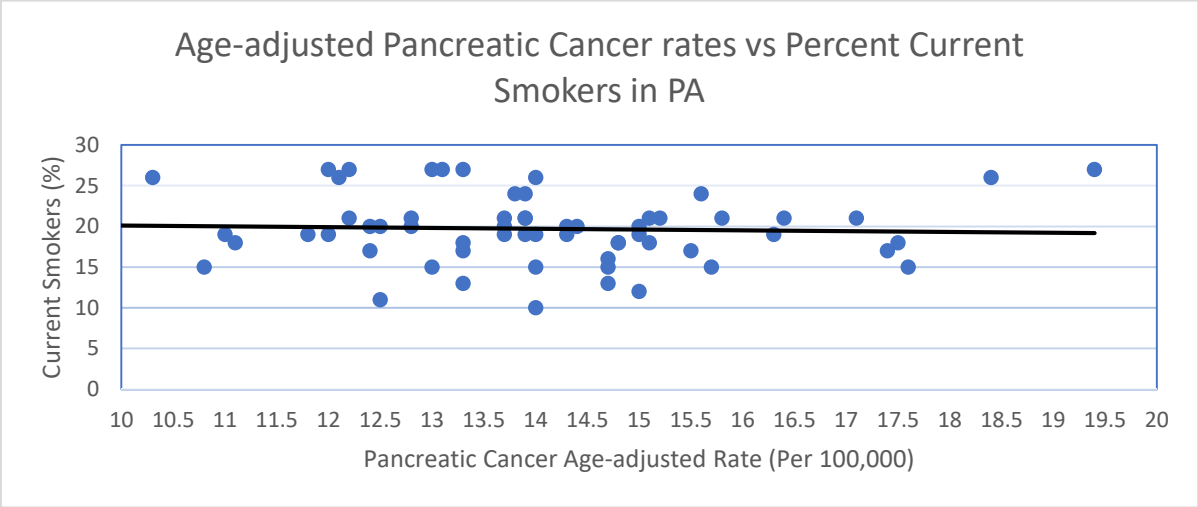


Figure 3 Age-Adjusted Rates of PC vs. Smoking Rates by County, Pennsylvania

Age-adjusted incidence rates of pancreatic cancer and obesity had a correlation of -0.11 with a p-value of <0.001 (Figure 4). The R^2 value for Figure 4 was 0.012.

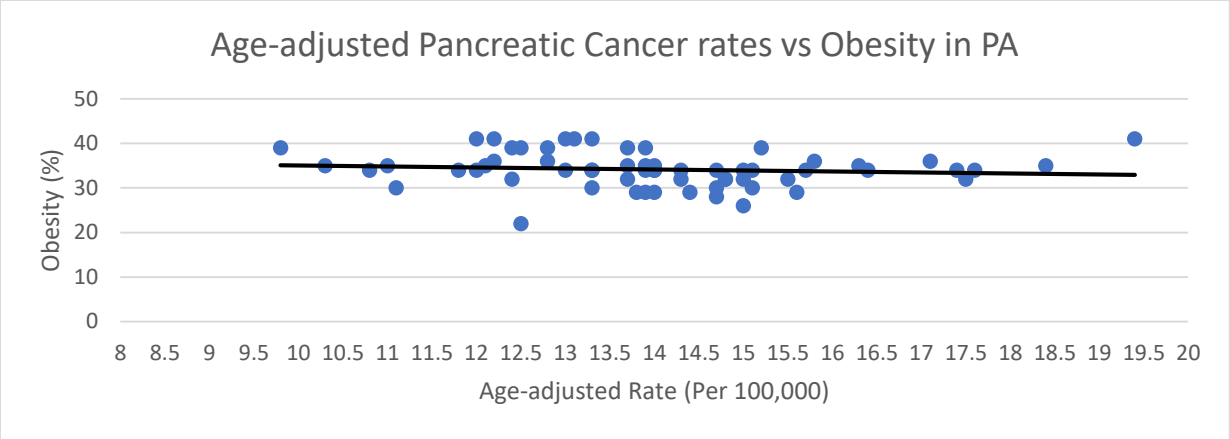


Figure 4 Age-Adjusted Incidence Rates of PC vs. Obesity Rates by County, Pennsylvania

Age-adjusted rates of pancreatic cancer and prevalence of diabetes had a correlation of -0.17 with a p-value of <.001 (Figure 5). The R^2 value for Figure 5 was 0.03.

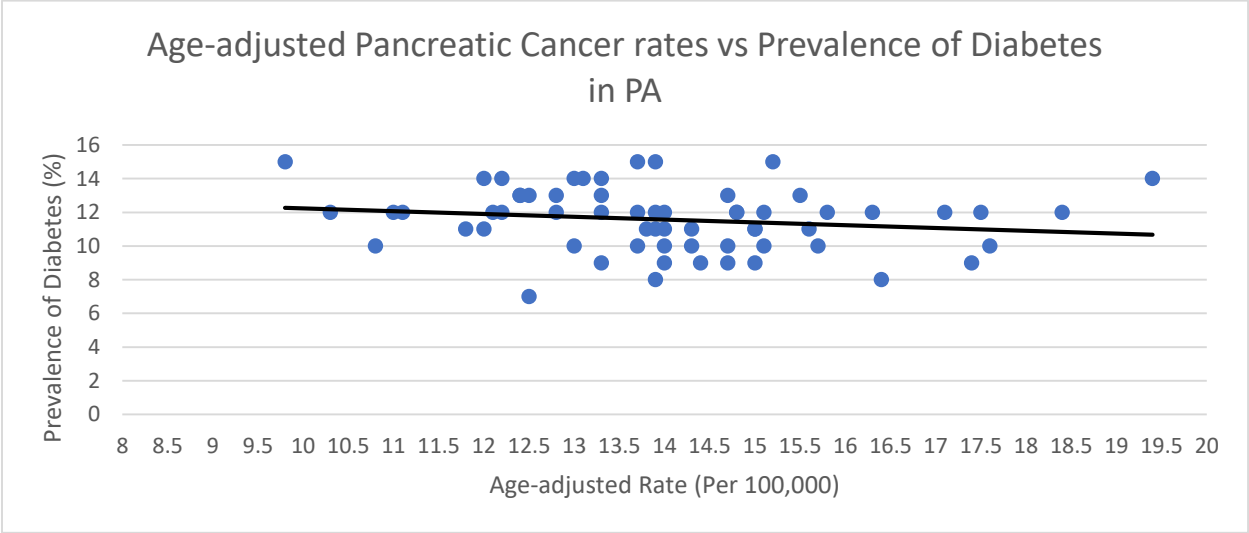


Figure 5 Age-Adjusted Incidence Rates of PC vs. Diabetes Rates by County, Pennsylvania

3.4.2 Allegheny County Zip Code Analysis

We sought to determine if there was a significant positive correlation of obesity and smoking with these rates. The data showed that for both sets of correlations, obesity and smoking modeled rates were positively associated with an increase in pancreatic cancer rates. Obesity rates had a correlation with pancreatic cancer incidence rates for Allegheny County zip codes of 0.279 ($p = .025$) and smoking modeled rates had a Spearman correlation of .247 ($p = .041$) (Table 3). The two independent variables also had a significant correlation with each other. When these two variables were considered together in a multiple linear regression, the overall model was significant, explaining 8.9% of the variance with the two variables (Table 2). They are collinear, indicating that obesity and smoking in a population often are found in the same group of people.

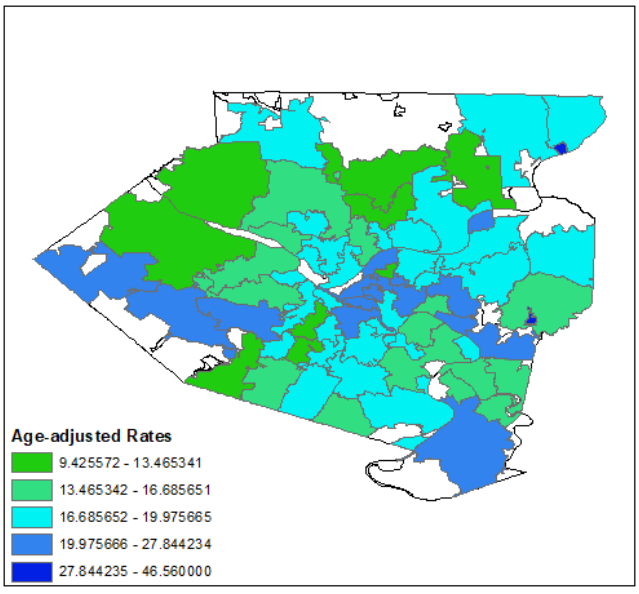


Figure 6 Age-Adjusted Incidence Rates of PC by Zip Codes in Allegheny County, Pennsylvania

Of the 97 zip codes in Allegheny County, 63 had zip codes with over 10 cases of pancreatic cancer from 2008-2017 and were included in the map (Figure 6). The range of age-adjusted incidence rates of pancreatic cancer was from 9.42 to 46.56 cases per 100,000 people.

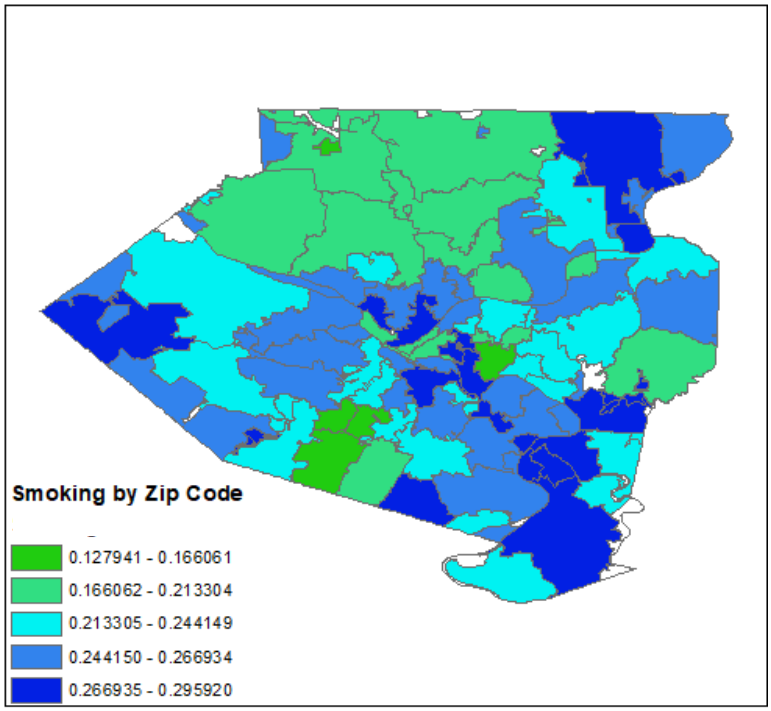


Figure 7 Obesity Rates by Zip Code in Allegheny County, Pennsylvania

All of the 97 zip codes in Allegheny County were used in the map (Figure 7). The ranges of smoking rates, defined as a proportion (0 to 1), were from 0.12 to 0.30

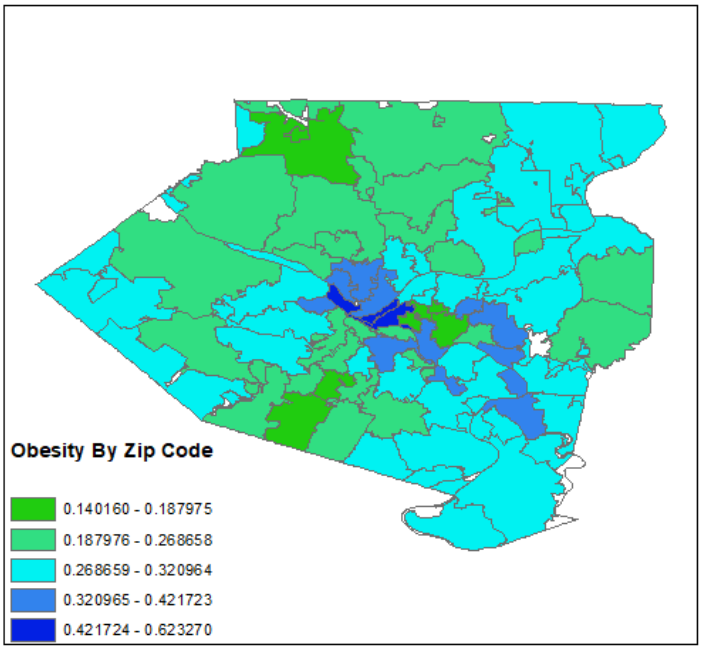


Figure 8 Obesity Rates by Zip Code in Allegheny County, Pennsylvania

All of the 97 zip codes in Allegheny County were used in the map. The ranges of obesity rates, defined as proportion (0 to 1), were from 0.14 to 0.62.

Table 2 Summary of Pearson and Spearman Correlation Tests For Age-Adjusted Rates of PC, Diabetee Rates, and Smoking Rates in Allegheny County

Correlations					
			Cancer	Obesity	Smoking
Spearman's rho	cancer	Correlation Coefficient	1.000	.249*	.248*
		Sig. (2-tailed)	.	.039	.040
		smoking	69	69	69
	obesity	Correlation Coefficient	.249*	1.000	.509**
		Sig. (2-tailed)	.039	.	.000
		N	69	97	97
	smoking	Correlation Coefficient	.248*	.509**	1.000
		Sig. (2-tailed)	.040	.000	.
		N	69	97	97

Model Summary				
Model	R	R^2	Adjusted R^2	Std. Error
1	0.299	0.089	0.062	5.072

ANOVA					
Model 1	Sum of Squares	df	Mean Square	F	Significance
Regression	166.14	2	83.070	3.229	0.046
Residual	1697.71	66	25.723		
Total	1863.85	68			

Coefficients					
	Unstandardized Coefficients		Standardized Coefficients		
Model 1	B	Std. Error	Beta	t	Significance
(Constant)	7.90	4.17		1.89	0.063
Obesity	12.95	11.85	0.15	1.09	0.28
Smoking	28.1	19.63	0.20	1.43	0.16

Model Summary				
Model	R	R2	Adjusted R2	Std. Error
1	0.247	0.061	0.047	5.11

ANOVA (Obesity)					
Model 1	Sum of Squares	df	Mean Square	F	Significance
Regression	113.45	1	113.45	4.34	0.041
Residual	1750.39	67	26.13		
Total	1863.85	68			

ANOVA (Smoking)					
Model 1	Sum of Squares	df	Mean Square	F	Significance
Regression	113.43	1	135.43	5.25	0.025
Residual	1728.41	67	25.80		
Total	1863.85	68			

4.0 Discussion

4.1 Literature Review

4.1.1 Non-Modifiable Risk Factors

Among the studies of non-modifiable risk factors examined in the literature which examined pancreatic cancer risk outcomes, all of the studies found an increase in the outcome of risk of pancreatic cancer. When summarizing the findings of these studies, the non-modifiable risk factors BRCA mutations, blood type, somatic mutations, and pancreatitis were shown to have a positive association with risk of pancreatic cancer and a negative association with survival rates. Iqbal et al. found a statistically significant increase in incidence of pancreatic cancer among female BRCA mutation carriers (2012). However, Iqbal et al. did not find a significant increase of pancreatic cancer among male BRCA mutation carriers. This means that the results of this study, and subsequent interpretations, would not be applicable to men in the general population. However, more research on the difference in incidence by sex is warranted.

In a study of 107,503 health professionals from 1976 to 1996, Wolpin et al. observed that non-O blood groups were more likely to develop pancreatic cancer (2009). However, the generalizability of this study is questionable, due to the study's population of health professionals not being a reflection of the general population. In a study by Lowenfels, Maisonneuve, DiMagno et al. of 246 patients with pancreatitis, patients with hereditary pancreatitis have a high risk of pancreatic cancer several decades after the initial onset of pancreatitis (1997).

In a study by Blackford et al. (2009), mutations in the SMAD4 gene of pancreatic cancer patients were significantly associated with a shorter overall survival time in those patients compared to pancreatic cancer patients without a mutated SMAD4 gene (hazard ratio, 1.92; 95% CI, 1.20-3.05; p = 0.006). They found that patients with SMAD4 gene inactivation survived a median of 11.5 months, compared with 14.2 months for patients without SMAD4 inactivation. A study by Bournet et al. found similar results in overall survival time. In Bournet et al. (2016), patients with a patients with a KRAS/G12D, mutation had a significantly shorter OS (6 months; 95% CI: 6.4–9.7) compared with the other patients (OS: 9 months; 95% CI: 10–13; HR: 1.47; P=0.003). These results are interesting in that these genes, CDKN2A and KRAS, have similar roles in that they are both tumor suppressor genes that inhibit uncontrolled cell proliferation. When summarizing the results of the studies, the identified non-modifiable risk factors of BRCA1/BRCA2 mutations, blood type, somatic mutations, and pancreatitis can cause an increase in the risk of developing pancreatic cancer. Possible public health interventions could focus on increasing early screening for these risk factors, thus potentially catching the disease in its earliest stages which would potentially improve survival of diagnosed individuals.

While the results of these studies indicate that there is associations between non-modifiable risk factors and risk/survival of pancreatic cancer, there are some limitations or differences between the studies that need further examination. For example, some of the studies did not control or adjust for the same confounders as one another. Bournet et al. and Blackford et al. both used hazard ratios to compare overall survival, but age was the only variable that both studies adjusted for. The results of these studies would be more robust and generalizable if each study had

controlled or adjusted for the same variables. This was also seen in the studies examining the association between non-modifiable risk factors and risk of pancreatic cancer, in that age was the only controlled variable that was shared amongst the studies. Iqbal et al. and Lowenfels, Maisonneuve, DiMagno both controlled for country, but Lowenfels, Maisonneuve, DiMagno et al. also controlled for sex. Wolpin et al. controlled for age, similar to the previously mentioned studies, but also controlled for smoking, BMI, diabetes, and physical activity. Like the studies that examined overall survival, the results of these studies would be more robust had they all controlled for the same variables.

4.1.2 Modifiable Risk Factors

The studies examined in this review all showed associations with modifiable risk factors and the risk of pancreatic cancer. These associations are important in particular because the modifiable risk factors examined can all be changed or embraced through behavior. When summarizing the studies, the studies regarding obesity, diabetes, smoking, and alcohol intake found a positive association between the modifiable risk factors and risk of pancreatic cancer. In a study by Jiao et al. that examined the reported drinking habits of 470,681 participants, Jiao et al. found that more alcoholic drinks per day was associated with an increased relative risk of pancreatic cancer. In study by Lynch et al. of 3,020 participants (2009), Lynch et al. found that compared with never smokers, current smokers had a significantly elevated risk of pancreatic cancer. When comparing the results from Jiao et al. and Lynch et al., the risk of pancreatic cancer from smoking and alcohol intake increased with intensity and duration. This suggests that

behavioral changes, such as smoking cessation or alcohol cessation, could potentially decrease ones risk for pancreatic cancer.

Obesity, diet and diabetes were also found to be associated with risk of pancreatic cancer. In a study by Michaud et al. of 163,689 health professionals (2001), participants with a BMI ≥ 30 had a 72% increase in risk of pancreatic cancer compared to BMI < 23. However, the results of this study might not be generalizable to the general population because the study's population only consisted of health professionals. In a study by Nöthlings et al. of 215,000 participants (2007), researchers found that intake of total flavonols was associated with a reduced pancreatic cancer risk. Flavonols are found in high quantities in fruits and vegetables, suggesting that a high fruit and vegetable diet could have a protective effect against pancreatic cancer. When examining 1,445 patients with diagnosed pancreatic cancer, Pannala et al. (2008) found that diabetes was 14 times more likely in patients with pancreatic cancer. This suggests that diabetes could be a potential precursor to pancreatic cancer. When summarizing the results of these studies, behavioral changes could help decrease a person's risk of pancreatic cancer. Diet can influence ones risk for diabetes and obesity. In addition, physical activity has been shown to lower ones risk for diabetes and obesity. Diet could be an area for the use of primary interventions in reducing the risk of pancreatic cancer.

4.2 Pennsylvania County Analysis

When examining the associations between age-adjusted pancreatic cancer incidence rates and modifiable risk factors at the county level across Pennsylvania, the results differ from what was suggested in the literature. When comparing age-adjusted incidence rates of pancreatic cancer to rates of diabetes by county, the results showed a very weak negative correlation between age-adjusted incidence rates and rates of diabetes. While the correlation was shown to be statistically significant, the correlations had very low R^2 values suggesting the correlations did not explain the observed correlation. These results differ from the literature where in a study by Pannala et al. (2008), Pannala found that patients diagnosed with pancreatic cancer were 14 times more likely to have diabetes. In addition, a very weak negative association was found between age-adjusted incidence rates of pancreatic cancer and smoking. Similar to the comparison between age-adjusted rates of pancreatic cancer and diabetes, the association was found to be significant, but with a similarly low R^2 value. This association differs from the study presented in the literature where Lynch et al. (2009) found a significantly elevated risk of pancreatic cancer in smokers compared to never smokers (OR = 1.77; 95% confidence interval: 1.38, 2.26). This trend continues when comparing age-adjusted incidence rates of pancreatic cancer and obesity where the results show a very weak, negative correlation between age-adjusted incidence rates of pancreatic cancer and obesity. The correlation was show to be significant but had a very low R^2 value. These results differ from the study by Michaud et al. (2001) where they found a positive association between pancreatic cancer risk and obesity with an increment of 1 BMI unit (1 kg/m2) associated with a 5% increased risk of pancreatic cancer among men (RR, 1.05; 95% CI, 1.00-1.11) and a 3% increased risk among women (RR, 1.03; 95% CI, 1.00-1.07). While each comparison between

age-adjusted incidence rates of pancreatic cancer and the identified showed a negative correlation, these correlations do not suggest that diabetes, obesity, and smoking are protective against the risk of pancreatic cancer. In addition to the correlations being weak, the low R^2 values in each of the correlations suggest that the models used were not good at explaining the data trends.

There were limitations when comparing age-adjusted rates and the modifiable risk factors at the county level. One limitation was the different time frames at which the modifiable risk factors were measured compared to when the age-adjusted incidence rates of pancreatic cancer were measured. The variables rate of smoking, rate of obesity, and rate of diabetes that were used in the county-level analysis were collected from 2017 through 2019. The county-level age-adjusted incidence rates of pancreatic cancer were collected from 2013-2017. While pancreatic cancer is a rare cancer and the incidence rates do not drastically change year to year, the difference in time of measurement could explain the observed correlations. Another limitation would be the measurement methods of the risk factors. Smoking was measured as percent current smokers, which doesn't include former smokers or intensity of smoking. Prevalence of diabetes was measured through percentage of individuals ever told they had diabetes. This measurement does not specify whether a confirmed diagnosis of diabetes was given to the individuals. Percent obesity did not specify which test was used to diagnosis obesity, whether it was using BMI or other methods. Another limitation was that the county level data generalized the prevalence of the risk factors when there is variability within the counties. These limitations could have contributed to the very weak, negative associations with low R^2 values shown in the analysis.

4.3 Allegheny County Zip Code Analysis

When examining the results of the zip code level data from Allegheny County, there were moderate, positive associations between age-adjusted incidence rates of pancreatic cancer and smoking, and between age-adjusted incidence rates of pancreatic cancer and obesity. These results are similar to the results of the studies examined in this review, with higher rates of obesity and smoking being associated with higher age-adjusted incidence rates of pancreatic cancer. A reason for why the results of the Allegheny County zip code analysis showed a positive association and the Pennsylvania County analysis did not could potentially be due to the type of data was used. Large areas overlook the significant variability seen within regions. Zip code level data allows for analysis with more respect to the variability seen within regions.

However, there were limitations present in Allegheny County analysis. One limitation was that the some of the zip codes were censored due to low 10-year case counts. Even when using a 10-year time interval to capture the most zip codes, 34 of the zip codes in Allegheny County were censored from the analysis due to low 10-year case counts. This could cause the maps to not accurately portray the true age-adjusted incidence rates across the county. Another limitation was the time intervals used for the zip code level analysis. The zip code pancreatic case counts were measured over a 10-year time interval however, the variables smoking and obesity were measured over a 4-year time interval. This limitation would affect the calculated correlations as the rates for the predictor variable smoking and obesity might not have been accurate rates for the zip codes, compared to the age-adjusted incidence rates of pancreatic cancer.

4.4 Public Health Significance

Pancreatic cancer is a major public health concern in Pennsylvania and in the United States. Pancreatic cancer's silent nature means that most people with pancreatic cancer are asymptomatic. When an individual begins starts to experience symptoms and finally undergoes testing, their cancer is often found in the distant phase. In the distant phase, the cancer has metastasized to other parts of the body. At this phase, the survival rate for pancreatic cancer is incredibly low. Despite being a rare cancer, the silent nature of pancreatic cancer contributes to its high mortality rate. This review examines modifiable and non-modifiable risk factors that could be used as early detectors for pancreatic cancer. The non-modifiable risk factors, such as BRCA1/BRCA2 mutations, blood type, somatic mutations in the p53/SMAD4/CDKN2A genes, and pancreatitis could be used as potential biomarkers during early screening. Modifiable risk factors, such as smoking, obesity, diabetes, diet, and alcohol intake, are shown in this review to be areas for primary interventions. The analyses performed in this review show how risk factors, such as smoking and obesity, can be used as potential predictors for pancreatic cancer in a community such as a zip code. More research into using both non-modifiable and modifiable risk factors as areas for primary interventions is necessary as these interventions could be implemented in policy to help reduce the incidence and mortality rate of pancreatic cancer.

Appendix A Studies and Findings

Risk Factor, alphabetically	Participants (Description; N)	Period	Findings	Author(s) (year published), alphabetically within risk factor
Alcohol Intake	Ages 50-71; N = 470,681	1995-1996	Those who consumed 6 or more drinks per day, compared with light drinkers, had a relative risk of 1.55 (95% CI: 1.13, 2.13; p = 0.004) and 3 or more drinks per day had a relative risk of 1.45 (95% CI: 1.17, 1.80; p = 0.002)	Jiao et al. (2009)
BRCA1/BRCA2 Mutations	Women with a mutation for new cases of pancreatic cancer from 50 cohorts across 10 countries; N = 5089	2008	Statistically significant 2.4-fold increase in the incidence of pancreatic cancer in female BRCA mutation carriers (P = 0.03);	Iqbal et al. (2012)
	Patients that have been screened for family history of pancreatic cancer (FPC); relative of those screened; N(probands) = 476	1973-2000	Half the FPC probands (mean age, 61.6 ± 11.5 years) were defined by having an affected parent, 36% (mean age, 68.1 ± 10.2 years) by an affected sibling, 4% (mean age, 79.0 ± 11.1 years) by an affected child, and 10% (mean age, 69.4 ± 8.8 years) by a combination of parents, siblings, or children.	Petersen et al. (2006)
Blood Type	Health professionals from Nurse's Health Study (NHS) and Health Professionals Follow-up Study (HPFS); N = 107,503	1976-1996	Blood groups A, AB, or B were more likely to develop pancreatic cancer (adjusted hazard ratios for incident pancreatic cancer were 1.32 (95% CI = 1.02, 1.72), 1.51 (95% CI = 1.02 to 2.23), and 1.72 (95% CI = 1.25 to 2.38), respectively.	Wolpin et al. (2009)
Diabetes	Diagnosed pancreatic cancer cases and controls over age 18; N(cases) = 512, N(controls) = 933	2007	Diabetes was 14 times more likely in patients with pancreatic cancer as compared with controls (95% confidence interval, 8.7–21.5)	Pannala et al. (2008)
Diet	Men and Women ages 45-75; N = 215,000	1993-1996	Intake of total flavonols was associated with a reduced pancreatic cancer risk (relative risk for the highest vs. lowest quintile = 0.77, 95% confidence interval: 0.58, 1.03; p = 0.046).	Nöthlings et al. (2007)
Genetic Mutations (p53, CDKN2A, SMAD4, KRAS)	Pancreaticoduodenectomy patients; N = 89	1989-2007	SMAD4 gene inactivation was significantly associated with shorter overall survival (hazard ratio, 1.92; 95% CI, 1.20-3.05; p = 0.006). Patients with SMAD4 gene inactivation survived a median of 11.5 months, compared with 14.2 months for patients without SMAD4 inactivation	Blackford et al.. (2009)
	Patients diagnosed with pancreatic cancer; N = 219	2016	Patients with a G12D mutation had a significantly shorter OS (6 months; 95% CI: 6.4–9.7) compared with the other patients (OS: 9 months; 95% CI: 10–13; HR: 1.47; *P* =0.003)	Bournet et al. (2016)
	Patients with diagnosed pancreatic cancer; N = 1537	2000-2011	CDKN2A mutation carriers were more likely to have a family history of pancreatic cancer (*P* =0.003); cases who reported having a first-degree relative with pancreatic cancer, the carrier proportions were 3.3%	McWilliams et al. (2011)
Obesity	NHS and HPFS; N(HPFS) = 46,648, N(NHS) = 117,041	1976-1996	BMI ≥ 30 had 72% increase in risk of PC compared to BMI < 23; An increment of 1 BMI unit (1 kg/m2) was associated with a 5% increased risk of pancreatic cancer among men (RR, 1.05; 95% CI, 1.00-1.11) and a 3% increased risk among women (RR, 1.03; 95% CI, 1.00-1.07).	Michaud et al. (2001)
Pancreatitis	Patients with pancreatitis over 30 years of age; N = 246	1996	Cumulative risk of pancreatic cancer in these patients to age 70 years was 40% (95% CI = 9%–71%). Cumulative risk of cancer to age 70 years was approximately 75% (95% CI = 32%–100%)	Lowenfels, Maisonneuve, DiMagno (1997)
Smoking	Patients with pancreatic adenocarcinoma; N = 114	2008	Significantly more non-synonymous mutations in the carcinomas obtained from ever smokers (mean, 53.1 mutations per tumor; SD, 27.9) than in the carcinomas obtained from never smokers (mean, 38.5; SD, 11.1; P = 0.04)	Blackford et al. (2009)
	Only included prospecitve nested case-control studies; 12 cohorts; one case control; N(cases) = 1,481, N(controls) = 1539	1985-2001	Compared with never smokers, current smokers had a significantly elevated risk with an odds ratio (OR) = 1.77, 95% confidence interval (CI): 1.38, 2.26	Lynch et al. (2009)

Appendix B Study Designs

Author(s) (year published), alphabetically within risk factor	Study Design	Risk of Pancreatic Cancer	Controlled for:
Jiao et al. (2009)	Cohort	Increased	Smoking
Iqbal et al. (2012)	Prospective Cohort	Increased	Age, Country
Petersen et al. (2006)	Prospective Cohort	Increased	Age
Wolpin et al. (2009)	Prospective Cohort	Increased	Age, smoking status, BMI, physical activity, Diabetes
Pannala et al. (2008)	Case-Control	Increased	Age, sex, BMI, smoking, diabetes, weight loss
Nöthlings et al. (2007)	Cohort	Decreased	Smoking, age, history of diabetes
Blackford et al.. (2009)	Observational	Increased	Age, lymph node status, margin status, and tumor size
Bournet et al. (2016)	Prospective Study	Increased	Age, Progression of disease, CA 1909 levels
McWilliams et al. (2011)	Observational	Increased	Smoking status, family history of cancer
Michaud et al. (2001)	Prospective Cohort	Increased	Age, smoking
Lowenfels, Maisonneuve, DiMagno (1997)	Cohort	Increased	Age, sex, country
Blackford et al. (2009)	Retrospective Cohort	Increased	Age, gender
Lynch et al. (2009)	Case-Control	Increased	Sex, age, race, BMI, Diabetes

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