AN INQUIRY INTO THE ASSOCIATION OF PANCREATIC CANCER WITH OTHER DISEASES OF WESTERNIZATION

By

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ABSTRACT OF THE DISSERTATION

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Pancreatic cancer (PC) is one of the most lethal cancers in the Unites States (US). It ranks number four among the leading causes of cancer death, and number ten in cancer incidence. In the absence of effective screening and methods of early diagnosis, most pancreatic cancers are diagnosed at a late stage. It has an overall 5 year survival of only 6.7%, so improvements in identifying a risk profile for the cancer and new etiological knowledge are urgently needed. We used the Surveillance, Epidemiology, and End Results (SEER) and the SEER-Medicare database, in which the SEER database is matched to the Medicare database by the National Cancer Institute and CMS (Centers for Medicare & Medicaid Services), to study the association between pancreatic cancer and other chronic diseases: prior cancers, prior non-cancer chronic diseases, and new-onset and long-term diabetes. In chapter one, we performed a retrospective cohort study (1,755,816 Whites, 205,751 Blacks, 176,855 Asians, and 196,192 Hispanics for all sites of cancers) for analysis of standardized incidence ratio (SIR) dividing the observed number of new cases of pancreatic cancer in cohorts of survivors of other cancers by the

expected number of cases of pancreatic cancer based on age, gender, and race reference rates derived from SEER for the US general population. We found an interesting pattern of associations with other cancers such as ascending and hepatic flexure colon cancer (White: SIR=1.63, 95% CI 1.35-1.94, Black: SIR=1.89, 95% CI 1.15-2.91, Asian: SIR=1.39, 95% CI 0.63-2.63, and Hispanic: SIR=1.42, 95% CI 0.61-2.80) and stomach cancer (White: SIR=2.03, 95% CI 1.50-2.68, Black: SIR=1.37, 95%CI 0.55-2.82, Asian: SIR=1.49, 95% CI 0.79-2.55, Hispanic: SIR=2.05, 95% CI 0.98-3.77), but not colorectal cancer of sigmoid, junction, and rectum, and not lung, breast, or prostate cancers. SIR's for the association of other cancers with PC decline for cancers further down the gastrointestinal tract: bile duct 3.75 (95% CI: 2.22-5.93), gall bladder 3.26 (95% CI: 1.49-6.19), cecum 1.08 (95% CI: 0.86-1.34), ascending colon 1.54 (95% CI: 1.23-1.90), hepatic flexure 1.90 (95% CI: 1.32-2.66), transverse colon 1.01 (95% CI: 0/67=1.56), sigmoid colon 0.93 (95% CI: 0.76-1.13), rectum 0.86 (95% CI: 0.67-1.08). Our findings are consistent with the idea that Western diets rich in fats and proteins may stimulate more pancreatic exocrine secretion that could contribute to inflammation in the pancreas as well as other digestive organs. The strength of this hypothesis is that it might be testable through comparisons of pancreatic secretions in persons on high protein/fat and low protein/fat diets in rich and poor resource settings.

In chapter two, we did a case-control study with frequency matching on age and length of enrollment in traditional Medicare plans. 28,375 new histologically confirmed PC cases with at least two years of prior enrollment in Medicare Parts A and B were identified. Potential controls were drawn from a 5% random sample of Medicare

enrollees who were living in the same SEER-defined geographic areas and met the same enrollment criteria. Controls were frequency matched to cases on age and length of enrollment in a 1:5 ratio (28,375 cases, 141,875 controls). Our findings confirmed male gender and Black race as important risk factors for pancreatic cancer (crude odd ratio of female vs. male: 0.72, 95% CI 0.71-0.74, Black vs. White: 1.24, 95% CI 1.19-1.30). Other minority groups, whose lifestyles may differ from the dominant White pattern, had lower risk (crude odd ratio: 0.74, 95% CI 0.68-0.81). After adjustment for age, gender, and race, the strongest association of PC was with pancreatitis (OR=5.37, 95% CI: 4.98-5.78), implying role of inflammation induced by pancreatic digestive enzymes, in carcinogenesis. These enzymes are secreted into the small intestine and presumably are progressively degraded as they move distally. Odds ratios for the association of PC with inflammatory disease decline as one moves down the GI tract: pancreatitis 5.37, liver diseases 2.07 (95% CI: 1.94-2.20), appendicitis 1.60 (95% CI: 1.30-1.95), diverticulitis 2.30 (95% CI: 2.21-2.39). Most of the chronic diseases that we tabulated are believed to be associated with Western lifestyles or related risk factors and several were associated with pancreatic cancer (adjusted odd ratio of coronary heart disease 1.44, 95% CI 1.38-1.50, hyperlipdemia 2.27, 95% CI 2.20-2.33, hypertension 2.08, 95% CI 2.02-2.13, COPD 1.52, 95% CI 1.45-1.56, diabetes 1.89, 95% CI 1.83-1.95, asthma 1.42, 95% CI 1.34-1.50; adjusted by age, gender, race/ethnicity, and length of enrollment in Medicare). Atherosclerosis of the pancreatic and coronary blood supplies is likely correlated and could explain the association. These associations are only of moderate strength, but the multiplicity of associations suggests several aspects of Western lifestyles might

contribute to pancreatic cancer risk. The associations with the atopic diseases would also support this view. The protective effect of dementia, which has been reported before, seems likely to be factitious but deserves further study.

In chapter three, we used SEER-Medicare database as in chapter two to perform a case-control study with 1:5 frequency matching on age and length of enrollment (cases: 24,004, controls: 120,020), but categorized diabetes into new-onset diabetes that occurred within two years of diagnosis of pancreatic cancer and long term diabetes known to have been present for more than two years. In this very large population-based case-control study of older Americans, we found highly significant, adjusted odds ratios of 2.07 (95% CI 2.00-2.15) and 1.46 (95% CI 1.35-1.49) for diabetes of >2 years and <=2 years duration, respectively. The robust association between diabetes and pancreatic cancer is not clearly understood and remains an important target for further investigation. It is notable that in the SEER Medicare population the prevalence of diabetes of greater than two years duration in both cases and controls exceeded the prevalence of diabetes of shorter duration in each race and ethnic group examined. These findings suggest that if future screening for pancreatic cancer is to target persons with diabetes, that all such persons, not just those with diabetes of recent onset, should be considered.

We suggest that Western high fat/protein diet promotes increased secretion of pancreatic enzymes contributing to tissue inflammation in GI tract sites as people age. This could be tested in small bowel aspirates in people eating Western and non-Western diets. Atherosclerosis in the coeliac and other relevant arteries could reduce blood flow

and weaken tissue resistance to exocrine secretions within the pancreas. Arterial plaques could be assessed by review of imaging studies done for PC and for other conditions. Our studies are based on the SEER cancer registries and the Medicare claims database, which both lack exposure records for environmental and dietary risk factors as well as for genetic traits. So the associations found could be confounded by differences in these other characteristics, which is an important limitation here. Although we selected population from 1992 to 2012 in the study of relationship between pancreatic cancer and other prior cancers, some individual prior cancer were too few for analysis after stratification by race and ethnicity, gender, age groups, and subtypes of cancer, which is another limitation in our study.

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THESIS INTRODUCTION

Pancreatic cancer is one of the most lethal cancers; it ranks number four among the leading causes of cancer death, and number ten in incidence in the US.[1,2] The estimated new cases in 2014 are 46,420, or 2.8% of all new cancer cases, and the estimated deaths, 39,590, comprise 6.8% of all cancer deaths. In the US, Blacks have higher incidence of pancreatic cancer than Whites (Black Male: 17.2, and Black Female 14.2 vs., White male 14.0, and White female 10.7, per 100,000), while Asians have lowest incidence (Male: 10.7, Female: 8.9, per 100,000). [1] The age-adjusted death rate of pancreatic cancer increased rapidly from 1930 to 1970, but slowed down since 1970; and from 2006 to 2010 the death rate increased 0.4% per year, while incidence rate increased 1.3%.[3] Despite stable incidence in US, the old age group (70-79 years) has higher increase in incidence (47%) compared with in 50-59 years age group (12%) from time period of 1977-1981 to 1997-2001. [4]

Pancreatic cancer is the 12th most common cancer worldwide, with about 338,000 new cases diagnosed in 2012, or 2% of the total new cancer cases; [5] its overall incidence and mortality have been stable d from 1992 to 2002.[6] Worldwide, pancreatic cancer incidence in developed countries is estimated 2 to 3 fold higher than developing countries based on International Agency for Research on Cancer (IARC) and Globacan project. In Africa the estimated incidence of pancreatic cancer is below 5 ASR (Age-Standardized Rates, based on world population) per 100,000 (the highest is 4.7 ASR per 100,000 in Libya, and lowest 1.8 ASR per 100,000 in Botswana); In Asia, the incidence varies by country, but can be roughly divided into two groups of higher and lower

incidence: the higher group (5.0-9.5 ASR per 100,000) includes Armenia, Japan, Israel, Kazakhstan, Korea, and Singapore, while lower group (< 5.0 ASR per 100,000) include the most of other countries such as Turkey, Jordan, and China with incidence (3-4 per 100,000). Like Asia, America has higher and lower groups of pancreatic cancer incidence: the higher incidence countries (6.0-8.0: ASR per 100,000) include French Guyana, Uruguay, USA, Argentina, Canada, the lower incidence countries (<= 5.0 ASR per 100,000) include Chile, Cuba, Brazil, and Mexico. Most countries in Europe have higher incidence, with the highest country being the Czech Republic (9.7 ASR, per 100,000), and lowest being France (7.5 ASR per 100,000). Oceania countries have lower incidence of below 3.0 ASR per 100,000 except Australia (6.6 ASR per100, 000), New Caledonia (6.5 ASR per 100,000), and New Zealand (5.9 ASR per 100,000).[5] The higher incidences of pancreatic cancer in developed countries imply that Western lifestyle may play an important role in pancreatic cancer etiology. However, pancreatic cancer is not easy to diagnose in the absence of modern medical diagnostics, so that some of the apparent difference in rates could result from under-diagnosis in resource-poor countries.

Consistent evidence shows smoking, old age (60-80 years), male gender, chronic pancreatitis, diabetes, and family history are risk factors of pancreatic cancer. Although food with high energy content, red meat, body mass index (BMI), and physical activity have been studied as individual risk factors in pancreatic cancer, the results have not been conclusive. [7-10] It is estimated 5-10% of pancreatic cancer has a familial or hereditary basis, the known subsets of familial pancreatic cancer include germline PRSS1

mutations (hereditary pancreatic pancreatitis), BRAC2 mutations in association with breast-ovarian cancer syndrome, CDKN2 mutations (atypical mole and multiple melanoma), or DNA repair gene mutation (ATM and PALB2). Although genetic risk and family history are important for pancreatic cancer, their importance in old people may decline compared with young individuals. [11] The most common type of pancreatic cancer (>90%) is infiltrating ductal adenocarcinoma, which is derived from exocrine cells of the pancreas, while neuroendocrine tumors that (2-3%) arise from islet cells comprise 2-3%. In this study we focus on pancreatic adenocarcinoma which has an overall 5 year survival of only 6.7%. In the absence of effective screening and methods of early diagnosis, most pancreatic cancers are diagnosed at a late stage.[1] These dismal statistics emphasize the importance of better understanding the causes of pancreatic cancer so that strategies for primary prevention can be developed. Since identifying risk factors directly has been difficult, we try here to study the association of pancreatic cancer with other prior cancers and with other prior chronic non-cancer diseases to enrich the risk profile.. Since pancreatic cancer and other cancer or non-cancer chronic disease share genetic and environmental risk factors, finding association between pancreatic cancer and other prior primary cancer or non-cancer chronic disease may give us some new clues to the etiology of pancreatic cancer. Thus, the broad aim of our study is to investigate the pancreatic cancer risk factors through analysis of the association between pancreatic cancer and other prior cancers (Chapter 1), prior non-cancer chronic diseases (Chapter 2), as well as long-term diabetes and new-onset diabetes (Chapter 3).

Chapter 1: Association of pancreatic cancer and other prior primary cancer

INTRODUCTION

With increased survival of cancer patients, more persons have the opportunity to develop a second (or third) primary cancer. As of January 1, 2005, there were 880,300 patients out of the 11 million cancer patients, or 8%, who developed multiple primary cancers. [12] In men, the top ten first primary cancer sites are prostate, colon and rectum, urinary bladder, melanoma, kidney and renal pelvis, oral cavity and pharynx, lung and bronchus, non-Hodgkin lymphoma, leukemia, and thyroid; in women, they are breast, colon and rectum, uterine corpus, melanoma, lung and bronchus, thyroid, ovary, urinary bladder, non-Hodgkin lymphoma, and uterine cervix. The longer the survival is, the more likely the development of subsequent cancer. Although there is a 14% increased risk of developing a second malignancy in cancer survivors compared with the general population, the subsequent cancers are varied and related to the type of first cancer and its treatment, environmental risk factors, and genetic factors. [12] Both pancreatic cancer and prostate cancer have high incidence in elderly Black males, both are related with the BRCA gene, [11] and both seem to be associated with Western lifestyle. However patients with prostate cancer show no increased risk of developing pancreatic cancer (RR=0.90, 95% CI: 0.25-2.31 for ages 20-49 years; RR=0.91, 95% CI: 0.79-1.03 for ages 50-64 years; and RR=1.03, 95% CI: 0.96-1.11 for ages >= 65 years). [13] Moreover, the trends of these two diseases are different in the US. From 1970 to 2010 the age-adjusted incidence of pancreatic cancer was stable around 15 per 100,000, while the

age-adjusted incidence rate of prostate cancer increased from 1975 (150 per 100,000) to 2007 (250 per 100,000). The increase between 1970s and 1988 was probably explained by the widespread use of transurethral resection for benign prostate hypertrophy (BPH) and associated incidental diagnosis of prostatic cancer, and the dramatic increase between 1980s and 1996 was due to the introduction of prostate-specific antigen (PSA) screening, however, the steadily increasing trend since 1996, [14] still contrasts with the stable trend in pancreatic cancer. Obesity is related to pancreatic cancer, but not much to prostate cancer, [15] which implies the risk profile is different for pancreatic cancer and prostate cancer. Amin et al studied incidence of pancreatic cancer in patients with non-pancreatic primary cancer based on SEER data from 1973 to 200., They found for age 20-49 years, the relative risk of pancreatic cancer was sharply increased in persons with ascending colon cancer (RR 4.62, 95% CI, 1.86-9.52), cancer of hepatic flexure (RR, 5.42, 95% CI, 1.12-15.84), cancer of biliary system (RR, 13.14, 95% CI, 4.27-30.66), and was moderately increased for breast cancer (RR, 1.32, 95% CI, 1.09-1.59), uterine cancer (RR, 1.61, 95% CI, 1.02-2.41), testes cancer (RR, 2.78, 95% CI, 1.83-4.05), and cancer of hematopoietic system (RR, 1.83, 95% CI, 1.28-2.53; among age 50-64 years, stomach cancer (RR, 1.88, 95% CI, 1.13-2.93), colon cancer of hepatic flexure (RR, 2.25, 95% CI, 1.08-4.13), lung and bronchus cancer (RR, 1.46, 95% CI, 1.16-1.82), pharynx cancer (RR, 2.26, 95% CI, 1.13-4.04), and bladder cancer (RR, 1.24, 95% CI, 1.03-1.48); among patients 65 years and older, stomach cancer (RR, 1.79, 95% CI, 1.23-2.53), colon cancer of hepatic flexure (RR, 1.76, 95% CI, 1.06-2.75), cancer of biliary system (RR, 2.35, 95% CI, 1.17-4.20), and uterus cancer (RR, 1.23, 95% CI, 1.03-1.47). [13]

However, the association between pancreatic cancer and other digestive cancers could be early sign of underlying pancreatic cancer. Another study found that 13.8% patients diagnosed with pancreatic cancer had extrapancreatic malignancies such as breast cancer, prostate cancer, colorectal, renal, as well as gynecologic tumors, [16] suggesting complex interaction or interrelationship of pancreatic cancer with other cancers because of shared environmental and/or genetic risk factors. It is likely that different aspects of Western lifestyle contribute to the genesis of different cancers with some aspects contributing to more than one type of cancer.

In this chapter, we explore the association of pancreatic cancer with other cancers (breast, prostate, ovarian, uterine corpus, and colorectal) that are more frequent in western societies than in developing countries. This study may provide clues as to what aspect of western lifestyle contributes to the excess pancreatic cancer seen in market economies. We use the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) which is an authoritative source of information on cancer incidence and survival in the United States. SEER currently collects 400,000 malignant cases annually and publishes cancer incidence from population-based cancer registries covering approximately 26 percent of the US population.[17]

METHODS

Design and Population

We used SEER to retrospectively define cohorts of persons with specific common cancers seen in the U.S. and to analyze the standardized incidence ratio (SIR) for

pancreatic cancer in these groups of cancer survivors.. SEER covers the entire age range from infancy to 85+ years. To allow consistency with data for chapter-2 and 3 which utilize the SEER-Medicare database, we stratified the study population by age < 65 years and age >= 65 years. For pancreatic cancer, the histological type ICD-O-3 included 8010-8012,8015,8020-8022,8140-8141,8143,8147,8210-8211,8230-8231,8260-8263,8440,8450,8452-8453,8470-8471,8480-8481,8490,8503-8504,8507-8508,8510,8514,8521,8560,8562,8570-8576 used by Amin et al, [13] and the description of code was listed in Appendix A based on the SEER website. [18]

Data Source and Study Variables

SEER cancer registries include SEER incidence and population data associated by age, sex, race, year of diagnosis, and geographic areas. [17] SEER coverage includes 26 percent of African Americans, 38 percent of Hispanics, 44 percent of American Indians and Alaska Natives, 50 percent of Asians, and 67 percent of Hawaiian/Pacific Islanders.[19] SEER research data exclude identifying information on individual patients and are available for public use. Data can be downloaded from SEER website with a signed Research Data Agreement that requires all research results to be presented or published in a manner that ensures that no individual can be identified. In addition, there must be no attempt either to identify individuals from any computer file or to link with a computer file containing patient identifiers.

For our study, we used SEER files based on SEER 13 Research Data (1992-2012) in SEER*Stat Database, the most recent data available for analysis of standardized incidence ratio (SIR). The SEER 13 registries consist of registries: Atlanta, Connecticut,

Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah with data available from 1973, plus Los Angeles and San Jose-Monterey with data available from 1992, plus Rural Georgia and the Alaska Native Tumor Registry with data available from 1992. SEER 13 Research Data (1992-2012) was released April 2015 and based on the November 2014 submission. [20] The data details are as below:

- Covers approximately 13.4% of the US population (based on 2010 census)
- Most geographic coverage available
- Associated referent rates are for subsequent primary cancer diagnoses
- Associated referent rates are available by expanded race (white, black, AI/AN, and API) and Hispanic ethnicity (Hispanic and non-Hispanic)
- Contains one record for each of 4,057,213 tumors

We used MP-SIR/SMR Sessions of SEER*Stat software version 8.2.1 for analysis of standardized incidence ratio (SIR) in conjunction with referent incidence rate files by age (5 year intervals), sex, and race, representing general US population. [21]

Standardized incidence ratio (SIR) of pancreatic cancer events in the population and in cohorts of other cancers compared to the general US population

Since pancreatic cancer is a lethal disease, most other primary cancer occur prior to pancreatic cancer, so we limit our analysis to the situation where the other cancer occurs first. This has the advantage that treatment of pancreatic cancer cannot affect the associations under study, but not the possibility that treatment of the other cancer might affect incidence of pancreatic cancer. With this study design we try to explore

the association of pancreatic cancer with other cancers, but do not infer that these are direct causal relationships. Therefore, although total follow-up time is used to calculate expected incidence, formal survival analysis is not done.

Population or cohorts of other cancers

We use other cancers diagnosed from 1992 to 2011 based on SEER database, and follow-up period from 1993 to 2012, stratified by each cancer (breast, prostate, ovarian, uterine corpus, colorectal, and other cancers) to form respective cohorts. Depending on overall association and available sample size, stratification by gender and race may be performed to create subcohorts.

General population

The population estimates furnished by SEER for its various participating registries are used to calculate incidence rate of pancreatic cancer.

Observed cases of pancreatic cancer

We accept pancreatic cancer diagnosed as a second (or subsequent) primary cancer during follow-up period of 1993 to 2012 based on SEER database in the cohorts of other cancers. We require a 12 month latency period to avoid pancreatic cancer that was diagnosed at a similar time with the other cancer and, thus, may reflect diagnostic confusion. We only include pancreatic cancer diagnosed at least 12 months after the diagnosis of the other cancer.

Expected cases of pancreatic cancer

We estimated expected cases and incidence rate of pancreatic cancer based on age, gender, and race specific referent rate files for the general population during the same period of 1993 and 2012.

Standardized incidence ratio (SIR)

The SIR is calculated as the observed incidence rate divided by the expected incidence rate. If SIR > 1, it indicates an elevated risk of pancreatic cancer for the cohort or subcohort; otherwise if SIR<1, it indicates reduced risk in the cohort or subcohort.

Statistical analysis

The MP-SIR/SMR Sessions of SEER*Stat software (Version: 8.2.1) provide two methods for estimating statistical significance: 1. Approximate method, and 2. Exact method. We selected the exact method for our study because of the small number of pancreatic cancer cases in some cohort or subcohort especially when further stratification by age group, gender, and race was created. The 95% confidence interval was calculated based on Byar's approximation which is most close to exact Poisson method. [22]

RESULTS

Colon cancer

In the colon cancer (excluding rectum) cohort, Whites and Asians have moderately higher risk of pancreatic cancer (SIR: 1.14 and SIR: 1.40) than the general US population, but this was not seen among Blacks (SIR: 1.01, 95% CI: 0.74-1.34), and Hispanics (SIR: 1.07, 95% CI: 0.71-1.55) (Table 1a and Figure 1). The risk was significant in younger White male (SIR: 1.47) (Table 1a), and younger Asian male (SIR: 2.85, 95% CI:

1.42-5.10) (Appendix 2b). Whites with right-sided colon cancer (ascending colon and hepatic flexure cancers combined) were at increased risk of pancreatic cancer (SIR: 1.63), particularly in younger males (SIR: 2.84) (Table 1b). The left-sided colon cancers (sigmoid, rectosigmoid junction, and rectum combined) were not associated with risk of pancreatic cancer in Whites (SIR: 0.90) (Table 1c), but Asians with cancer of the hepatic flexure through the sigmoid colon were at higher risk of pancreatic cancer (SIR: 1.75, 95% CI: 1.24-2.41) (see Appendix 1a). Black people with rectal cancer seemed to have higher risk of pancreatic cancer (SIR: 1.36, 95% CI: 0.72-2.33), but not in Whites (SIR: 0.86, 95% CI: 0.67-1.08) and Asian (SIR: 0.81, 95% CI: 0.35-1.60) (Appendix 1a). Similar to Whites, Blacks with right-sided colon cancer had 89% higher risk (SIR: 1.89) of pancreatic cancer (Table 1b), especially in Black women (SIR: 2.21) (Appendix 1c), but almost no increased risk with left-sided colon cancer (Table 1c).

Breast cancer

In the cohort of female breast cancer (Table 2 and Figure 2), we found that Asian women had moderately higher risk of pancreatic cancer (SIR: 1.38) than Asian women in the general US population, especially in older age groups (SIR: 1.63, 95% CI: 1.22-2.14) (Appendix 3a) compared with younger age (SIR: 1.01, 95% CI: 0.63-1.53) (Appendix 2a). In contrast, younger Black women with breast cancer had higher risk of pancreatic cancer (SIR: 1.37, 95% CI: 1.02-1.80) (Appendix 2c), but not in older Black women (SIR: 0.89, 95% CI: 0.64-1.20) (Appendix 3c). White females with breast cancer, no matter in which age group, did not showed increased risk (SIR: 1.01) (Table 2 and Figure 2); neither did Hispanic women (SIR: 0.95) (Table 2).

Prostate cancer

Table 4 and Figure 2 indicated that Asian male with prostate cancer had little higher risk of pancreatic cancer (SIR: 1.24), the risk was weak in Black (SIR: 1.08), and almost no risk in White male (SIR: 0.94) as well as Hispanic male (SIR: 0.83).

Stomach cancer

Table 4 and Figure 1 showed that prior stomach cancer in Whites was associated with two fold higher risk of pancreatic cancer (SIR: 2.03) and was statistically significant. Risk was also elevated in Black (SIR: 1.37), Asian (SIR: 1.49), and Hispanic (SIR: 2.05) ethnicities, although these did not reach statistical significance. People with stomach cancer at a young age had more than 3 fold increased risk of pancreatic cancer (White male: SIR: 3.63 in younger group vs. SIR: 2.19 in older group) (Table 4).

Cancers of gallbladder, intra hepatic, and extra hepatic bile duct

Although people with liver cancer were not at increased risk of pancreatic cancer compared to the general US population, in persons surviving cancer of gallbladder, the risk was strikingly elevated in all three ethnicities examined(White SIR: 3.26, 95% CI: 1.49-6.19; Black SIR: 13.68, 95% CI: 3.68-35.02; Asian SIR: 4.12, 95% CI: 0.46-14.88) (Appendix 1a). White male with gallbladder cancer had significant risk of pancreatic cancer (SIR: 7.63, 95% CI: 2.46-17.81) (Appendix 1b) compared with White female (SIR: 1.90, 95% CI: 0.51-4.86) (Appendix 1c), especially in younger male (SIR: 19.33, 95% CI: 3.89-56.48) (Appendix 2b). In Blacks, females had substantially increased risk of pancreatic cancer (SIR: 18.73, 95% CI: 5.04-47.95) (Appendix 1c). In addition, Whites with cancer of intra hepatic or extra hepatic bile duct had higher risk (SIR: 3.75, 95% CI:

2.22-5.93) of pancreatic cancer than the general population (Appendix 1a), especially in younger female (SIR: 8.02, 95% CI: 1.61-23.43) (Appendix 2c) and male (SIR: 5.75, 95% CI: 1.85-13.42) (Appendix 2b).

Uterine and ovary cancer

White women with uterine cancer in older age had decreased rates of pancreatic cancer (SIR: 0.80, 95% CI: 0.63-1.00) whereas older Black women (SIR: 1.42, 95% CI: 0.68-2.61) and older Asian women (SIR: 1.52, 95% CI: 0.61-3.13) had increased rates (Appendix 3c). Among younger women, no increased risk was observed and no difference among White, Black, and Asian was found (Appendix 2c). In the cohort with ovarian cancer, younger White females had significantly higher risk of pancreatic cancer (SIR: 1.75, 95% CI: 1.11-2.63) (Appendix 2c) that was not seen in the older age group (SIR: 0.87, 95% CI: 0.51-1.39) (Appendix 3c). Black, Asian, and Hispanic women with ovary cancer did not showed increased risk of pancreatic cancer.

Lung cancer

In the cohort of lung and bronchus cancer, Table 5 and Figure 1 showed that White people had moderate higher risk (SIR: 1.25) than the general US population, especially among younger White men and women (SIR: 1.85 and SIR: 1.68). The association was not significant in Blacks (SIR: 0.99) and Asians (SIR: 0.87) or Hispanics (SIR: 0.94).

DISCUSSION

Cancers of Western Lifestyle

Our study showed that the different cohorts of prior specific cancers had different risks of pancreatic cancer depending on race and ethnicity, gender, and age. Although patients with prior cancers related to Western lifestyle such as colon cancer, especially the right-sided colon cancer, and breast cancer had increased risk of pancreatic cancer at least in some populations, patients with prior cancers related to smoking such as stomach cancer, lung cancer, and bladder cancer also showed increased risk of pancreatic cancer in some populations.

In the colon cancer (excluding rectum) cohort, Whites and Asians had moderately higher risk of pancreatic cancer than the general US population, especially in younger male. Wynder el at had reported that the up-trend of mortality rates of colon cancer and pancreatic cancer were parallel in Japan from 1955 to 1985 when Japanese adopted Western lifestyle, such as increased intake of red meat. [23] When we divided colon cancer into the right-sided (ascending and hepatic flexure) and left-sided colon cancer (sigmoid, rectosigmoid, and rectum), we found that the right-sided colon cancer was associated with increased the risk of pancreatic cancer 1.39 to 2.84 times, but left-sided colon cancer was not. In the US, the right-sided or proximal colon cancers composed 42% of colon cancer, although both right-sided and left-sided colon cancer showed an stable trend in 1990s and declining trend since 2000, the right-sided colon cancer decreased more slowly than the left-sided colon cancer.[24] A recent publication reported that from 2009 to 2013 the colorectal cancer incidence rate of proximal colon was 16.9 per 100,000 persons, distal colon 9.0, rectum 11.5, and other locations 3.2; males had higher rate than females for each location within the colon. [25] The right-sided

and left-sided colon cancers might be related to the different embryological origin, physiological mechanism, and genetic mutational pathways of two locations. [26] Right-side colon cancer is more related to risk factors such as smoking, less physical activity, family history, and bacteria invasion than is left-sided. [27,28] Asians with cancer of hepatic flexure colon through sigmoid colon had 75% higher risk of pancreatic cancer. Colorectal cancer shares some risk factors with pancreatic cancer, such as obesity or higher BMI, smoking, heavy alcohol drinking, red meat or processed meat consumption, and less fruit and vegetable intake. [29,30] Asians with both right-side (hepatic flexure) and left-side (sigmoid) colon had higher risk of pancreatic cancer than the general US population, which might be related to heterogeneity of Asian populations. The varied incidences of colorectal cancer in persons from different original countries of Asia may suggest the importance of consumption of red meat for colorectal cancer risk. [31,32] In Blacks, male gender and young age are more likely to have left-site or distal colon cancer while women are more likely to develop right-site or proximal colon cancer, [33-35] our findings showed Blacks with right-sided colon cancer had 89% higher risk of pancreatic cancer, which was mainly attributable to the association in women.

Breast cancer is considered to be a Western disease; however in our study White and Hispanic women with breast cancer did not show increased risk of pancreatic cancer. Asian women with breast cancer had 38% higher risk of pancreatic cancer than Asians in the general US population, especially when people having breast cancer in older age (SIR: 1.63). There may be more variation in the extent to which these older Asian women have adopted Western lifestyles than exists among the other groups.

Breast cancer in young Black women is known to have more aggressive biological characteristics than in other black and white women, so that the 37% higher risk for pancreatic cancer in this group is hard to interpret. . Compared to Whites, both Asian and Black women have lower incidence of breast cancer, but black women have higher prevalence of obesity and higher BMI level, and lower age at the first birth in contrast with White and Asian women. [36, 37] Obesity is a risk factor for pancreatic cancer. [38] In the US, White women usually have breast cancer subtype $HR^+/HER2^-$, whereas a larger proportion of cancers in Black women are $HR^-/HER2^-$ (triple negative), and in Asian women are $HR^+/HER2^+$. [39] The HR^+ cancer is associated positively with nulliparity, menopausal hormone therapy, and longer duration between menarche and first birth.[40] Lee et al reported that estrogen hormone therapy was negatively associated with pancreatic cancer, although no association was found with combined estrogen and progestin therapy, as well as reproductive risk factors such as age at menarche, parity, breastfeeding, and age at menopause. [41] Among Asian women, use of hormone therapy is low, [42] which might help to explain the higher risk of pancreatic cancer in Asian women with breast cancer.

In the cohorts of prostate cancer, another Western disease, Asian and Blacks had little higher risk of pancreatic cancer. However, White with prostate cancer had slightly lower risk of pancreatic cancer. Older Hispanic males with prostate cancer had 41% lower risk of having pancreatic cancer. Prostate cancer and pancreatic cancer share common risk factors such as age, race of African American, and increased level of insulin-like growth factor, but not smoking. [43,44, 45] Interestingly, in our study, we found

similar increased risk of pancreatic cancer in Asian men with prostate cancer and Asian women with breast cancer, especially among the older people. Changes of hormone profile may play a role; it reported that increased testosterone is associated with prostate cancer, [46] and testosterone might be involved in development of pancreatic cancer. [47] The comparative study by Wu et al showed the levels of total and bioavailable testosterone were highest in Asian-Americans, compared with African-Americans, and whites. However, the DHT (Dihydrotesterone): testosterone ratio was highest in African-Americans followed by whites, and Asian, [48] which might be related to higher risk of pancreatic cancer among Asian men with prostate cancer. We found protective effect of prostate cancer to pancreatic cancer in White, which is consistent with findings of Davis EJ.et al. They suggested the phenomenon might be related to the enhanced surveillance and screening for other cancers in prostate cancer patients, [49] but the significantly lower risk of pancreatic cancer in Hispanic prostate cancer patients might have other unknown factors involved. [50, 51]

Other Cancers

Although stomach cancer rates are generally low in Western countries, in our study Whites with prior stomach cancer had two fold increased risk of pancreatic cancer compared to the general US population. Black and Asian with stomach cancer had 37% and 49% higher risk respectively. In Hispanic, the risk also was increased two fold. People with stomach cancer in younger age had higher risk of pancreatic cancer than people with stomach cancer in older age. Although the trend of stomach cancer incidence has declined for decades in the US, the cancers of the gastric cardia cancer

increased in both White male (2.1 to 3.3 per 100,000 person-years) and Black male (1.0 to 1.9 per 100,000 person-years) from 1974-1976 to 1992-1994, and stomach cardia cancer accounted for almost 50% of all stomach cancers in White male and close to 20% in Black male.[52] These patterns were stable from 1992 to 2012. [53] In Japan the cancer of the upper third of stomach increased in men from 1975 to 1989, while the cancer of the lower third of stomach decreased. [54] Moreover, the risk profile of distal or intestinal type of stomach cancer is different from proximal or cardia location of stomach cancer [55]. The intestinal or non-cardia type is associated with Black race, Helicobacter pylori Infection, alcohol drinking, and smoking; while cardia type with White, high social economic status, obesity, and gastroesophageal reflux disease [55, 56, 57, 58, 59, 60, 61]. Studies show pancreatic cancer is also associated with Helicobacter pylori infection and N-Nitrosamine exposure [62, 63], although both pancreatic cancer and stomach cancer shares some genetic trait such as type A of ABO blood group, Lynch syndrome, and Peutz-Jegher syndrome, genetic factor or familiar history contribute less than 10% of cases in both cancers. Moreover, ABO blood type usually needs to interact with environmental risk factor such as Helicobacter pylori infection to cause cancer [64, 65, 11, 66, 67]. It may be worth investigating the type of stomach cancer associated with pancreatic cancer in the major US ethnic groups.

Pancreatic cancer and gallbladder cancer share common risk factors such as obesity, older age, and H pylori infections, but gender distribution is just the opposite; females are more likely to get gallbladder cancer compared to males, (ratio 3:1), while males have higher risk of pancreatic cancer than females. A major risk for gallbladder

cancer is a medical history of gallstone and cholecystitis, which are also related to pancreatic cancer. [68, 69, 70] In our study White men, especially younger men, had significant risk of developing pancreatic cancer compared with White women. In contrast, Black women had significantly higher risk of pancreatic cancer than Black men. Whites, especially younger Whites with cancer of intra hepatic or extra hepatic bile duct had higher risk of pancreatic cancer than the general US population. Intra-hepatic and extra-hepatic cholangiocarcinoma has similar risk profile as gallbladder cancer, but males are more likely than females to get cholangiocarcinoma. [71, 72, 73] We suspect the close anatomical locations of gallbladder, liver, and pancreas might facilitate sharing of local pathological risk factors such as inflammation and immune response among those organs, and the longer the inflammation and altered immune response exists, the more likely people will develop pancreatic cancer.

White women with uterine cancer in older age showed mild protective effect for pancreatic cancer, compared with older Black women with 42-52% higher risk. Among women with early menarche, later menopause, or higher BMI, the risk of uterine cancer increased, but smoking which is a risk factor for pancreatic cancer is inversely related to uterine cancer. [74] The adult smoking rate in White women (17.8%) is higher than Black (15.4%) and Asian women (4.8%), [75] which might affect the association between uterine cancer and pancreatic cancer.

Black, Asian, and Hispanic women with ovary cancer did not showed increased risk of pancreatic cancer even in younger age group. The risk factors of ovary cancer are mostly unknown, it seems there is no association with smoking and BMI, but a few

studies found higher C-reactive protein (CRP) level and depression might be related to ovary cancer. [74] The relationship between CRP and pancreatic cancer is ambiguous, [76, 77] but depression might be a potential pancreatic cancer risk factor. [78]

Smoking is aa very strong risk factor for lung cancer and a modest risk factor for pancreatic cancer and Long smoking duration increases risk of both cancers. [79, 80] In the cohort of lung cancer, we found 78% higher SIR for pancreatic cancer in White people which is likely explained by smoking. However, the association was not seen in Black, Asian, and Hispanic groups. The race differences in SIR are difficult to explain only by smoking, [81] it might be related to diet such as inadequate Vitamin D intake. [82, 83]

Interesting positive associations from this analysis include the association of pancreatic cancer with gastric cancer and cancers of the ascending colon and hepatic flexure as well as with cancer of the gall bladder and bile ducts. While dietary exposures are a likely cause of changing rates of colon and gastric cancer associated with Westernization, the pancreas is not directly exposed to the food stream, so the influence of diet on the pancreas (and gall bladder) would have to be indirect. Nevertheless, since nutritional differences between low resource and rich countries are large, and since the pancreas is a digestive organ, it is tempting to posit dietary differences as a likely cause of difference in pancreatic cancer incidence. Dietary fat and protein, which stimulate pancreatic secretion, are some of the most obvious nutritional differences between rich and poor countries, and we hypothesize that greater stimulation of exocrine secretions may cause low level inflammation and increase the incidence of pancreatic cancer. Increased concentrations of lipases and proteases in the

bowel could also cause or exacerbate inflammation of other exposed, cancer-prone parts of the gastrointestinal tract. Inflammation is a known risk factor for a number of cancers as illustrated by large organ-specific risks associated with pancreatitis, inflammatory bowel disease, Helicobacter and cholecystitis. The powerful inflammatory potential of increased pancreatic exocrine secretions could potentially reflux into the stomach and gall bladder and probably also reach the proximal part of the colon. The stronger association of pancreatic cancer with right-sided than left-sided colon cancer would also be consistent with this hypothesis, and would support a generic effect of rich diets to the development pancreatic cancer rather than a specific effect of red meat, which has been associated with left-sided colon cancer. Kim el al reported recently the fat intake was positively associated with proximal colon cancer, especially the intake of saturated fatty acid (SFA) with adjusted OR of 1.78 (95% CI: 0.95-3.32) for men, and 1.41 (95% CI: 0.57-3.49) for women, while the association between SFA and distal colon cancer was weaker (adjusted OR: 1.56, 95% CI 0.80-3.11), especially among women (adjusted OR: 0.64, 95% CI 0.21-1.97). [84] SFA intake was associated 36% higher risk of pancreatic cancer, and SFA from animal source had 43% higher risk based on a large cohort study.[85]

The absence of associations between pancreatic cancer and breast cancer suggests that differences in reproductive physiology (menarche, age at childbearing, parity, age at menopause, breastfeeding, use of exogenous estrogen, oral contraceptive) between rich and poor countries probably are not much related to the cause of pancreatic cancer. Likewise, prostate cancer, which has increased enormously

with Westernization, would seem to have different aspect of lifestyle change driving that increase. Although smoking is a known risk factor for pancreatic cancer, the association with lung cancer was only weak.

In considering our findings, we are cognizant of the great predominance of experience in the US White population that has been available to us. Thus, much of the above discussion really reflects the findings in that part of the population. Findings in the black community are largely consistent with the white experience, and the numbers are so small among Hispanics that inferences are limited. In Asians numbers are also limited, but pancreatic cancer appears to be associated more broadly with several other diseases of Westernization. This may be because of the substantial number of Asians who were born abroad and who may be acculturating to Western life style across a range of behaviors and exposures.

We studied other prior cancer cohorts such as bladder cancer, kidney cancer, lymphoma, leukemia, and melanoma. Because of the small case numbers of pancreatic cancer in those cohorts, we do not discuss those cancers here. We performed sensitivity analysis for latency period of 6 months and 24 months, and got results that were similar to those reported herein for the 12 month latency period used above, thus implying there was little confusion between prior primary cancers and subsequent pancreatic cancer.

CONCLUSION

This is an exploratory study but has found an interesting pattern of associations with other cancers that is consistent with the idea that Western diets rich in fats and

proteins may stimulate more pancreatic exocrine secretion that could contribute to inflammation in the pancreas as well as other digestive organs. The strength of this hypothesis is that it might be testable through comparisons of pancreatic secretions in persons on high protein/fat and low protein/fat diets in rich and poor resource settings.

This is a study of population-based cancer registry, which lacks both exposure records of environment and genetic risk factors, so the associations found areindirect. Prior cancers proxy for unspecified risk factors associated with lifestyle, which is definitely a major limitation here. Although we selected population from 1992 to 2012, some cohort samples of individual prior cancer were too small for analysis after stratification by race and ethnicity, gender, age groups, and subtypes of cancer, which is another limitation in our study.

TABLES and FIGURES

TABLE 1a. OCCURRENCE OF PANCREATIC CANCER IN PATIENTS WITH COLON CANCER (Excluding Rectal Cancers)

	N	O/E	LCL	UCL
White	376	1.14	1.03	1.26
Black	47	1.01	0.74	1.34
Asian	45	1.40	1.02	1.87
Hispanic	28	1.07	0.71	1.55
White Only				
Male	215	1.25	1.09	1.43
Age <65	64	1.47	1.13	1.88
Age 65+	151	1.18	1.00	1.38
Female	161	1.02	0.87	1.19
Age <65	32	1.27	0.87	1.79
Age 65+	129	0.98	0.82	1.36

Note: O/E=observed pancreatic cancers/expected number;
LCL = lower 95% confidence limit on O/E;
UCL = Upper 95% confidence limit on O/E.

TABLE 1b. OCCURRENCE OF PANCREATIC CANCER IN PATIENTS WITH CANCER OF ASCENDING COLON AND HEPATIC FLEXURE

	N	O/E	LCL	UCL
White	121	1.63	1.35	1.94
Black	20	1.89	1.15	2.91
Asian	9	1.39	0.63	2.63
Hispanic	8	1.42	0.61	2.80
White Only				
Male	76	2.11	1.66	2.64
Age <65	21	2.84	1.76	4.34
Age 65+	55	1.93	1.45	2.51
Female	45	1.17	0.85	1.56
Age <65	4	1.17	0.31	3.00
Age 65+	41	1.21	0.87	1.64

See footnotes to Table 1a

TABLE 1c. OCCURRENCE OF PANCREATIC CANCER WITH COLORECTAL CANCER:SIGMOID/JUNCTION/RECTUM

	N	O/E	LCL	UCL
White	212	0.90	0.78	1.03
Black	30	1.11	0.75	1.58
Asian	34	1.18	0.82	1.65
Hispanic	22	1.03	0.64	1.55
White Only				
Male	126	0.90	0.75	1.08
Age <65	46	1.02	0.75	1.36
Age 65+	80	0.85	0.67	1.06
Female	86	0.89	0.71	1.09
Age <65	20	0.89	0.54	1.37
Age 65+	66	0.89	0.69	1.13

See footnotes to Table 1a

TABLE 2. OCCURRENCE OF PANCREATIC CANCER IN WOMEN WITH BREAST CANCER

	N	O/E	LCL	UCL
White	722	1.01	0.94	1.09
Black	93	1.10	0.89	1.35
Asian	74	1.38	1.08	1.73
Hispanic	52	0.95	0.71	1.25
White Only				
Female	722	1.01	0.94	1.09
Age <65	270	1.07	0.95	1.21
Age 65+	452	0.98	0.89	1.07

See footnotes to Table 1a

TABLE 3. OCCURRENCE OF PANCREATIC CANCER IN MEN WITH PROSTATE CANCER

	N	O/E	LCL	UCL
White	1,287	0.94	0.89	0.99
Black	258	1.08	0.95	1.22
Asian	106	1.24	1.02	1.50
Hispanic	101	0.83	0.68	1.01

See footnotes to Table 1a

TABLE 4. OCCURRENCE OF PANCREATIC CANCERIN PATIENTS WITH STOMACH CANCER

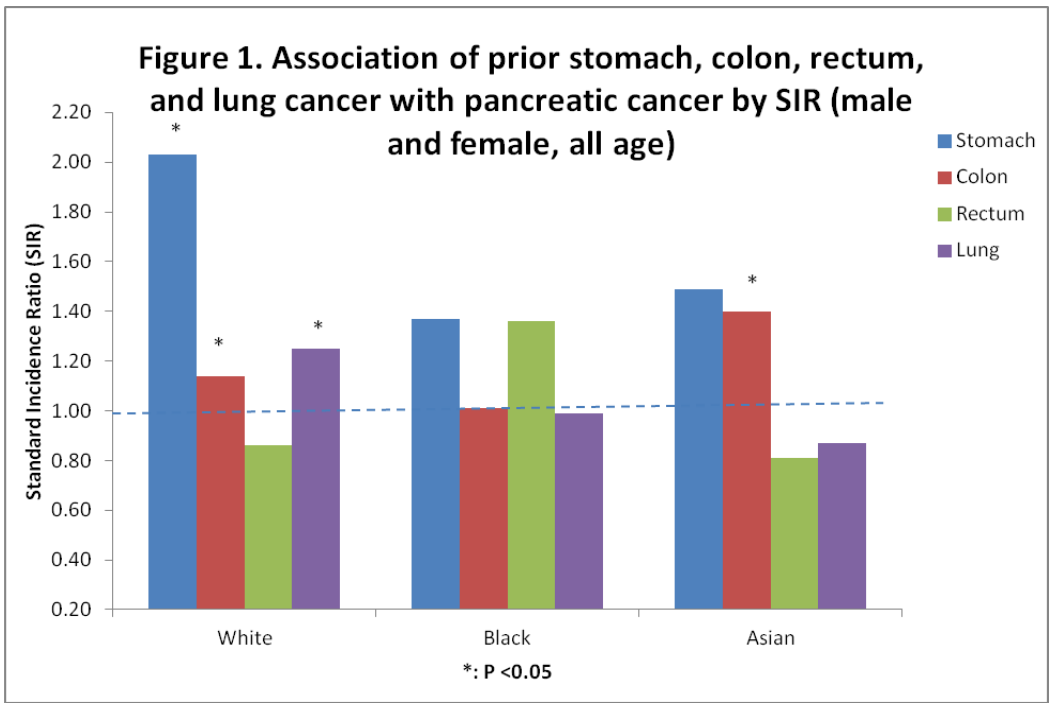
	N	O/E	LCL	UCL
White	49	2.03	1.50	2.68
Black	7	1.37	0.55	2.82
Asian	13	1.49	0.79	2.55
Hispanic	10	2.05	0.98	3.77
White Only				
Male	39	2.58	1.83	3.53
Age <65	15	3.63	2.03	5.99
Age 65+	24	2.19	1.40	3.26
Female	10	1.11	0.53	2.04
Age <65	1	0.61	0.01	3.39
Age 65+	9	1.21	0.55	2.30

See footnotes to Table 1a

TABLE 5. OCCURRENCE OF PANCREATIC CANCER IN PATIENTS WITH LUNG & BRONCHUS CANCER

	N	O/E	LCL	UCL
White	171	1.25	1.07	1.45
Black	19	0.99	0.60	1.55
Asian	10	0.87	0.42	1.60
Hispanic	7	0.94	0.38	1.94
White Only				
Male	90	1.27	1.02	1.56
Age <65	38	1.85	1.31	2.54
Age 65+	52	1.03	0.77	1.35
Female	81	1.24	0.98	1.54
Age <65	26	1.68	1.10	2.46
Age 65+	55	1.10	0.83	1.43

See footnotes to Table 1a



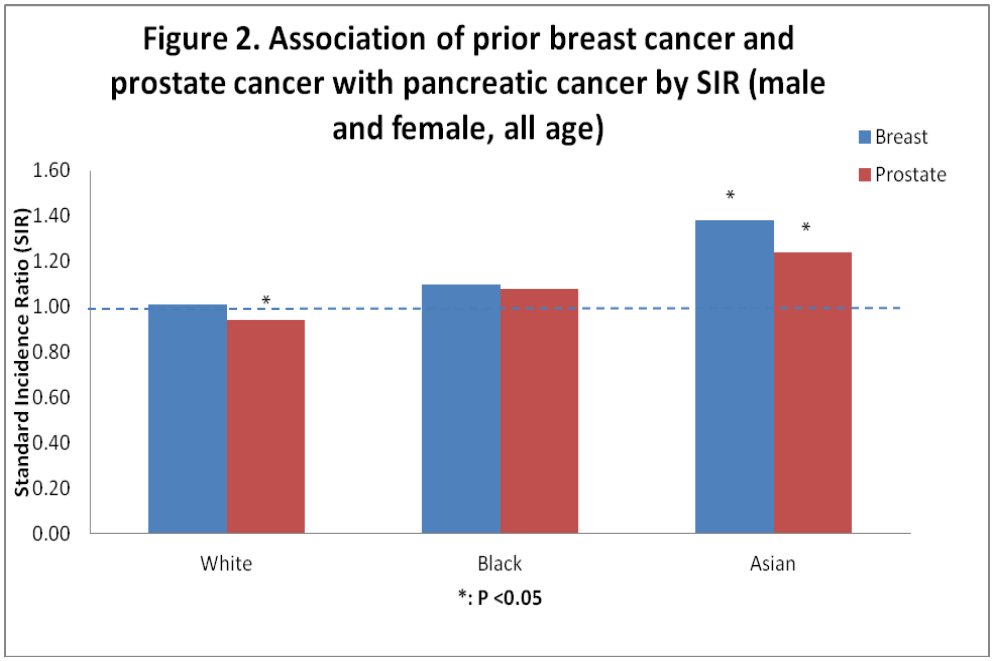


Figure 2. Association of prior breast cancer and prostate cancer with pancreatic cancer by SIR (male and female, all age)
Breast
Prostate
Standard Incidence Ratio (SIR)
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
*
*
*
White
Black
Asian
*: P <0.05

APPENDIX

Appendix A. Pancreatic cancer histology and behavior code description (behavior code of 3 means malignancy)

Histology	Histology Description	Histology/Behavior	Histology/Behavior Description
801	CARCINOMA, NOS	8010/3	Carcinoma, NOS
801	CARCINOMA, NOS	8011/3	Epithelioma, malignant
801	CARCINOMA, NOS	8012/3	Large cell carcinoma, NOS
801	CARCINOMA, NOS	8015/3	Glassy cell carcinoma
802	CARCINOMA, UNDIFF., NOS	8020/3	Carcinoma, undifferentiated type, NOS
802	CARCINOMA, UNDIFF., NOS	8021/3	Carcinoma, anaplastic type, NOS
802	CARCINOMA, UNDIFF., NOS	8022/3	Pleomorphic carcinoma
814	ADENOCARCINOMA, NOS	8140/3	Adenocarcinoma, NOS
814	ADENOCARCINOMA, NOS	8141/3	Scirrhous adenocarcinoma
814	ADENOCARCINOMA, NOS	8143/3	Superficial spreading adenocarcinoma
814	ADENOCARCINOMA, NOS	8147/3	Basal cell adenocarcinoma
821	ADENOCA. IN ADENOMA. POLYP	8210/3	Adenocarcinoma in adenomatous polyp
821	ADENOCA. IN ADENOMA. POLYP	8211/3	Tubular adenocarcinoma
823	SOLID CARCINOMA, NOS	8230/3	Solid carcinoma, NOS
823	SOLID CARCINOMA, NOS	8231/3	Carcinoma simplex
826	PAPILLARY ADENOCARCINOMA, NOS	8260/3	Papillary adenocarcinoma, NOS
826	PAPILLARY ADENOCARCINOMA, NOS	8261/3	Adenocarcinoma in villous adenoma
826	PAPILLARY ADENOCARCINOMA, NOS	8262/3	Villous adenocarcinoma
826	PAPILLARY ADENOCARCINOMA, NOS	8263/3	Adenocarcinoma in tubulovillous adenoma
844	CYSTADENOCARCINOMA, NOS	8440/3	Cystadenocarcinoma, NOS
845	PAPILLARY CYSTADENOCA., NOS	8450/3	Papillary cystadenocarcinoma, NOS
845	PAPILLARY CYSTADENOCA., NOS	8452/3	Solid pseudopapillary carcinoma
845	PAPILLARY CYSTADENOCA., NOS	8453/3	Intraductal papillary-mucinous carcinoma, invasive
847	MUCINOUS CYSTADENOCARC., NOS	8470/3	Mucinous cystadenocarcinoma, NOS
847	MUCINOUS CYSTADENOCARC., NOS	8471/3	Papillary mucinous cystadenocarcinoma
848	MUCINOUS ADENOCARCINOMA	8480/3	Mucinous adenocarcinoma
848	MUCINOUS ADENOCARCINOMA	8481/3	Mucin-producing adenocarcinoma
849	SIGNET RING CELL CARCINOMA	8490/3	Signet ring cell carcinoma
850	DUCT CARCINOMA	8503/3	Intraductal papillary adenocarcinoma with invasion
850	DUCT CARCINOMA	8504/3	Intracystic carcinoma, NOS
850	DUCT CARCINOMA	8507/2	Intraductal micropapillary carcinoma
850	DUCT CARCINOMA	8508/3	Cystic hypersecretory carcinoma
851	MEDULLARY CARCINOMA, NOS	8510/3	Medullary carcinoma, NOS
851	MEDULLARY CARCINOMA, NOS	8514/3	Duct carcinoma, desmoplastic type
852	LOBULAR AND OTHER DUCTAL	8521/3	Infiltrating ductular carcinoma

	CA.		
856	ADENOSQUAMOUS CARCINOMA	8560/3	Adenosquamous carcinoma
856	ADENOSQUAMOUS CARCINOMA	8562/3	Epithelial-myoepithelial carcinoma
857	ADENOCA. WITH METAPLASIA	8570/3	Adenocarcinoma with squamous metaplasia
857	ADENOCA. WITH METAPLASIA	8571/3	Adenocarcinoma w cartilag. & oss. metaplas.
857	ADENOCA. WITH METAPLASIA	8572/3	Adenocarcinoma with spindle cell mataplasia
857	ADENOCA. WITH METAPLASIA	8573/3	Adenocarcinoma with apocrine metaplasia
857	ADENOCA. WITH METAPLASIA	8574/3	Adenocarcinoma with neuroendocrine differen.
857	ADENOCA. WITH METAPLASIA	8575/3	Metaplastic carcinoma, NOS
857	ADENOCA. WITH METAPLASIA	8576/3	Hepatoid adenocarcinoma

Appendix 1a. Relationship between prior primary cancers and subsequent pancreatic cancer (male and female, all age)															
All age, 12 month latency period	White						Black				Asian				
Male and female	Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI	
All Sites	1,755,816	4,037	1.01	0.98	1.04	205,751	564	1.09	1.00	1.18	176,855	342	1.20#	1.08	1.33
Oral Cavity and Pharynx	41,202	81	1.09	0.87	1.35	4,579	13	1.79	0.95	3.06	5,308	4	0.66	0.18	1.69
Stomach	16,106	49	2.03#	1.50	2.68	2,866	7	1.37	0.55	2.82	5,500	13	1.49	0.79	2.55
Colon excluding Rectum	123,253	376	1.14#	1.03	1.26	16,708	47	1.01	0.74	1.34	15,705	45	1.40#	1.02	1.87
Cecum	28,401	83	1.08	0.86	1.34	4,119	10	0.85	0.41	1.56	2,202	3	0.62	0.12	1.81
Ascending Colon	20,773	87	1.54#	1.23	1.90	2,948	14	1.69	0.92	2.84	2,286	2	0.41	0.05	1.48
Hepatic Flexure	6,284	34	1.90#	1.32	2.66	788	6	2.59	0.95	5.64	746	7	4.35#	1.74	8.96
Transverse Colon	10,325	28	1.01	0.67	1.46	1,426	4	1.01	0.27	2.59	1,310	4	1.43	0.38	3.66
Sigmoid Colon	40,392	103	0.93	0.76	1.13	4,537	9	0.69	0.31	1.31	6,766	23	1.66#	1.05	2.49
Rectum	37,841	72	0.86	0.67	1.08	4,391	13	1.36	0.72	2.33	6,218	8	0.81	0.35	1.60
Gallbladder	2,100	9	3.26#	1.49	6.19	238	4	13.68#	3.68	35.02	346	2	4.12	0.46	14.88
Intrahep and Extrahep Bile Ducts, and Other Biliary	4,414	18	3.75#	2.22	5.93	373	0	0	NA	NA	1,008	3	3.67	0.74	10.72
Lung and Bronchus	109,184	171	1.25#	1.07	1.45	14,814	19	0.99	0.60	1.55	12,128	10	0.87	0.42	1.60
Melanoma of the Skin	97,573	167	0.92	0.79	1.07	468	0	0	NA	NA	908	1	0.91	0.01	5.06
Female Breast	328,281	722	1.01	0.94	1.09	37,470	93	1.1	0.89	1.35	37,539	74	1.38#	1.08	1.73
Corpus Uteri	63,506	131	0.88	0.74	1.04	5,331	15	1.25	0.70	2.06	6,897	12	1.36	0.70	2.38
Ovary	28,124	40	1.22	0.87	1.66	2,284	2	0.65	0.07	2.35	3,304	2	0.73	0.08	2.64
Prostate	364,089	1,287	0.94#	0.89	0.99	60,642	258	1.08	0.95	1.22	28,632	106	1.24#	1.02	1.50
Urinary Bladder	84,834	266	1.05	0.93	1.18	4,325	18	1.38	0.82	2.18	5,016	11	0.91	0.45	1.63
Kidney and Renal Pelvis	46,538	99	1.09	0.89	1.33	5,965	14	1.11	0.61	1.86	3,973	6	1.05	0.38	2.29
Thyroid	47,979	50	1.03	0.76	1.36	3,480	1	0.21	0.00	1.17	7,660	6	0.95	0.35	2.07
Non-Hodgkin Lymphoma	75,351	148	1.03	0.87	1.21	6,522	7	0.61	0.24	1.26	7,095	9	0.87	0.40	1.65
Leukemia	46,179	64	0.88	0.68	1.12	3,906	2	0.36	0.04	1.30	3,561	3	1.2	0.24	3.51

Appendix 1b. Relationship between prior primary cancers and subsequent pancreatic cancer (male, all age)															
All age, 12 month latency period	White						Black				Asian				
Male	Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI	
All Sites	903,870	2,441	1	0.96	1.04	111,807	370	1.12#	1.01	1.24	81,668	187	1.16	1.00	1.34
Oral Cavity and Pharynx	28,543	62	1.19	0.91	1.53	3,123	7	1.46	0.58	3.01	3,458	3	0.76	0.15	2.22
Stomach	10,005	39	2.58#	1.83	3.53	1,531	4	1.51	0.41	3.87	3,162	8	1.54	0.66	3.03
Colon excluding Rectum	60,856	215	1.25#	1.09	1.43	7,490	17	0.82	0.48	1.31	7,829	23	1.37	0.87	2.06
Cecum	12,549	41	1.15	0.83	1.56	1,742	3	0.62	0.12	1.81	958	1	0.47	0.01	2.62
Ascending Colon	9,539	52	1.93#	1.44	2.53	1,244	3	0.91	0.18	2.66	1,009	1	0.45	0.01	2.50
Hepatic Flexure	3,097	24	2.66#	1.70	3.96	361	3	2.79	0.56	8.15	367	4	5.09#	1.37	13.03
Transverse Colon	4,889	16	1.18	0.67	1.92	615	2	1.21	0.14	4.37	658	3	2.1	0.42	6.14
Sigmoid Colon	21,726	63	0.98	0.75	1.25	2,171	4	0.65	0.17	1.66	3,577	11	1.39	0.69	2.49
Rectum	21,808	44	0.86	0.62	1.15	2,274	9	1.79	0.82	3.40	3,677	5	0.84	0.27	1.96
Gallbladder	518	5	7.63#	2.46	17.81	58	0	0	NA	NA	116	0	0	NA	NA
Intrahep and Extrahep Bile Ducts, and Other Biliary	2,420	13	4.60#	2.45	7.87	180	0	0	NA	NA	533	1	2.46	0.03	13.69
Lung and Bronchus	54,498	90	1.27#	1.02	1.56	7,991	15	1.45	0.81	2.39	6,755	7	1.07	0.43	2.20
Melanoma of the Skin	53,637	99	0.84	0.68	1.02	211	0	0	NA	NA	447	0	0	NA	NA
Female Breast	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA
Corpus Uteri	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA
Ovary	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA
Prostate	364,089	1,287	0.94#	0.89	0.99	60,642	258	1.08	0.95	1.22	28,632	106	1.24#	1.02	1.50
Urinary Bladder	65,038	205	1.02	0.89	1.17	2,934	13	1.45	0.77	2.48	3,812	6	0.64	0.23	1.39
Kidney and Renal Pelvis	28,969	64	1.07	0.82	1.37	3,504	11	1.48	0.74	2.65	2,506	3	0.81	0.16	2.37
Thyroid	11,371	14	0.83	0.45	1.39	640	0	0	NA	NA	1,499	3	1.9	0.38	5.55
Non-Hodgkin Lymphoma	40,638	91	1.16	0.93	1.42	3,473	4	0.7	0.19	1.79	3,736	4	0.74	0.20	1.89
Leukemia	27,172	39	0.86	0.61	1.18	2,158	1	0.33	0.00	1.84	2,026	2	1.31	0.15	4.73

Appendix 1c. Relationship between prior primary cancers and subsequent pancreatic cancer (female, all age)															
All age, 12 month latency period	White						Black				Asian				
Female	Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI	
All Sites	851,946	1,596	1.01	0.96	1.06	93,944	194	1.03	0.89	1.19	95,187	155	1.25#	1.06	1.46
Oral Cavity and Pharynx	12,659	19	0.87	0.52	1.36	1,456	6	2.43	0.89	5.29	1,850	1	0.48	0.01	2.67
Esophagus	2,014	2	0.89	0.10	3.21	385	0	0	NA	NA	152	0	0	NA	NA
Stomach	6,101	10	1.11	0.53	2.04	1,335	3	1.22	0.25	3.56	2,338	5	1.43	0.46	3.34
Colon excluding Rectum	62,397	161	1.02	0.87	1.19	9,218	30	1.15	0.78	1.64	7,876	22	1.43	0.90	2.17
Cecum	15,852	42	1.01	0.73	1.37	2,377	7	1.02	0.41	2.10	1,244	2	0.74	0.08	2.67
Ascending Colon	11,234	35	1.18	0.82	1.64	1,704	11	2.21#	1.10	3.95	1,277	1	0.37	0.00	2.06
Hepatic Flexure	3,187	10	1.13	0.54	2.08	427	3	2.42	0.49	7.07	379	3	3.65	0.73	10.66
Transverse Colon	5,436	12	0.85	0.44	1.48	811	2	0.86	0.10	3.11	652	1	0.73	0.01	4.06
Sigmoid Colon	18,666	40	0.86	0.61	1.17	2,366	5	0.72	0.23	1.68	3,189	12	2.01#	1.04	3.51
Rectosigmoid Junction	7,080	18	1.04	0.62	1.64	827	1	0.44	0.01	2.45	1,081	1	0.52	0.01	2.89
Rectum	16,033	28	0.85	0.56	1.23	2,117	4	0.88	0.24	2.25	2,541	3	0.76	0.15	2.22
Gallbladder	1,582	4	1.9	0.51	4.86	180	4	18.73#	5.04	47.95	230	2	6.4	0.72	23.11
Intrahep and Extrahep Bile Ducts, and Other Biliary	1,994	5	2.52	0.81	5.88	193	0	0	NA	NA	475	2	4.85	0.54	17.51
Lung and Bronchus	54,686	81	1.24	0.98	1.54	6,823	4	0.45	0.12	1.15	5,373	3	0.61	0.12	1.78
Melanoma of the Skin	43,936	68	1.07	0.83	1.36	257	0	0	NA	NA	461	1	1.99	0.03	11.07
Female Breast	328,281	722	1.01	0.94	1.09	37,470	93	1.1	0.89	1.35	37,539	74	1.38#	1.08	1.73
Corpus Uteri	63,506	131	0.88	0.74	1.04	5,331	15	1.25	0.70	2.06	6,897	12	1.36	0.70	2.38
Ovary	28,124	40	1.22	0.87	1.66	2,284	2	0.65	0.07	2.35	3,304	2	0.73	0.08	2.64
Prostate	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA
Urinary Bladder	19,796	61	1.17	0.89	1.50	1,391	5	1.2	0.39	2.80	1,204	5	1.8	0.58	4.20
Kidney and Renal Pelvis	17,569	35	1.12	0.78	1.56	2,461	3	0.58	0.12	1.69	1,467	3	1.48	0.30	4.32
Thyroid	36,608	36	1.14	0.80	1.58	2,840	1	0.28	0.00	1.56	6,161	3	0.63	0.13	1.84
All Lymphatic and Hematopoietic Diseases	68,899	97	0.9	0.73	1.10	8,245	10	0.79	0.38	1.45	6,191	7	1.02	0.41	2.10
Hodgkin Lymphoma	6,779	6	1.54	0.56	3.35	950	1	1.9	0.02	10.57	439	0	0	NA	NA
Non-Hodgkin Lymphoma	34,713	57	0.86	0.65	1.11	3,049	3	0.52	0.10	1.52	3,359	5	1.02	0.33	2.38
Leukemia	19,007	25	0.9	0.58	1.33	1,748	1	0.38	0.00	2.11	1,535	1	1.04	0.01	5.79

Appendix 2a. Relationship between prior primary cancers and subsequent pancreatic cancer (male and female, age <= 64 years)															
Age <=64 yrs, 12 month latency period	White					Black					Asian				
Male and female	Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI	
All Sites	911,559	1,312	1.07#	1.01	1.13	124,731	235	1.09	0.96	1.24	97,457	102	1.32#	1.08	1.60
Oral Cavity and Pharynx	25,310	35	1.13	0.79	1.57	3,471	7	1.68	0.67	3.46	3,744	4	1.58	0.43	4.05
Stomach	7,007	16	2.78#	1.59	4.51	1,484	2	1.2	0.13	4.33	2,120	2	1.25	0.14	4.51
Colon excluding Rectum	43,492	96	1.40#	1.13	1.71	8,446	13	0.86	0.46	1.47	6,556	16	2.36#	1.35	3.83
Cecum	7,970	17	1.37	0.80	2.19	1,957	3	0.84	0.17	2.45	707	0	0	NA	NA
Ascending Colon	5,668	16	1.80#	1.03	2.92	1,365	5	2.11	0.68	4.92	725	0	0	NA	NA
Hepatic Flexure	1,757	9	2.95#	1.35	5.60	356	3	4.19	0.84	12.24	265	3	10.07#	2.02	29.42
Transverse Colon	3,262	7	1.33	0.53	2.74	691	0	0	NA	NA	514	1	1.9	0.02	10.57
Sigmoid Colon	17,256	29	0.99	0.66	1.42	2,482	2	0.42	0.05	1.52	3,173	9	2.59#	1.18	4.92
Rectum	19,285	21	0.79	0.49	1.21	2,847	6	1.39	0.51	3.03	3,603	3	0.95	0.19	2.78
Gallbladder	761	4	7.62#	2.05	19.51	128	2	23.66#	2.66	85.42	133	1	15.53	0.20	86.41
Intrahep and Extrahep Bile Ducts, and Other Biliary	1,877	8	6.43#	2.77	12.67	211	0	0	NA	NA	424	1	5.53	0.07	30.77
Lung and Bronchus	42,674	64	1.78#	1.37	2.27	7,915	12	1.59	0.82	2.78	4,863	3	1.26	0.25	3.68
Melanoma of the Skin	66,488	66	0.85	0.66	1.08	287	0	0	NA	NA	609	1	2.43	0.03	13.52
Female Breast	195631	270	1.07	0.95	1.21	26308	51	1.37#	1.02	1.80	26841	22	1.01	0.63	1.53
Corpus Uteri	36294	56	1.03	0.78	1.34	3197	5	1.01	0.33	2.36	5166	5	1.2	0.39	2.80
Ovary	17595	23	1.75#	1.11	2.63	1569	1	0.74	0.01	4.12	2543	2	1.57	0.18	5.67
Prostate	134,898	338	0.94	0.84	1.05	29,767	92	0.97	0.78	1.19	7,766	15	1.12	0.63	1.85
Urinary Bladder	29,150	57	0.91	0.69	1.18	1,887	4	0.92	0.25	2.36	1,579	5	2.3	0.74	5.37
Kidney and Renal Pelvis	26,563	36	1.08	0.76	1.50	4,024	8	1.32	0.57	2.60	2,259	1	0.53	0.01	2.95
Thyroid	41,333	31	1.12	0.76	1.59	2985	1	0.34	0.00	1.89	6,465	5	1.56	0.50	3.64
Non-Hodgkin Lymphoma	40,532	52	1.11	0.83	1.46	4,832	4	0.68	0.18	1.74	4,007	4	1.34	0.36	3.43
Leukemia	26,502	23	1.06	0.67	1.59	2,648	1	0.45	0.01	2.50	2,653	2	2.2	0.25	7.94

Appendix 2b. Relationship between prior primary cancers and subsequent pancreatic cancer (male, age <= 64 years)															
Age <=64 yrs, 12 month latency period	White					Black					Asian				
Male	Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI	
All Sites	432,252	753	1.04	0.97	1.12	63,860	140	1	0.84	1.18	36,075	49	1.41#	1.04	1.86
Oral Cavity and Pharynx	18,623	26	1.07	0.70	1.57	2,419	4	1.31	0.35	3.35	2,494	3	1.68	0.34	4.91
Stomach	4,619	15	3.63#	2.03	5.99	862	2	1.82	0.20	6.57	1,197	1	0.94	0.01	5.23
Colon excluding Rectum	24,321	64	1.47#	1.13	1.88	4,142	4	0.47	0.13	1.20	3,324	11	2.85#	1.42	5.10
Cecum	4,341	9	1.18	0.54	2.24	939	2	1.02	0.11	3.68	348	0	0	NA	NA
Ascending Colon	3,148	12	2.18#	1.13	3.81	635	0	0	NA	NA	364	0	0	NA	NA
Hepatic Flexure	1,025	9	4.74#	2.16	9.00	186	1	2.34	0.03	13.02	137	2	12.74#	1.43	46.00
Transverse Colon	1,852	4	1.24	0.33	3.17	332	0	0	NA	NA	273	1	3.5	0.05	19.47
Sigmoid Colon	9,699	21	1.11	0.69	1.70	1,271	1	0.37	0.00	2.06	1,611	6	3.00#	1.10	6.53
Rectum	11,775	16	0.88	0.50	1.43	1,552	4	1.54	0.41	3.94	2,189	3	1.42	0.29	4.15
Gallbladder	208	3	19.33#	3.89	56.48	31	0	0	NA	NA	45	0	0	NA	NA
Intrahep and Extrahep Bile Ducts, and Other Biliary	1,114	5	5.75#	1.85	13.42	112	0	0	NA	NA	241	0	0	NA	NA
Lung and Bronchus	21,883	38	1.85#	1.31	2.54	4,410	8	1.76	0.76	3.47	2,666	1	0.72	0.01	4.01
Melanoma of the Skin	34,375	39	0.76	0.54	1.04	128	0	0	NA	NA	288	0	0	NA	NA
Female Breast	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA
Corpus Uteri	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA
Ovary	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA
Prostate	134,898	338	0.94	0.84	1.05	29,767	92	0.97	0.78	1.19	7,766	15	1.12	0.63	1.85
Urinary Bladder	22,766	48	0.93	0.69	1.23	1,413	2	0.57	0.06	2.06	1,230	3	1.67	0.34	4.88
Kidney and Renal Pelvis	17,231	25	1.04	0.67	1.54	2,507	7	1.69	0.68	3.48	1,484	0	0	NA	NA
Thyroid	9,369	7	0.71	0.28	1.46	529	0	0	NA	NA	1,195	3	3.63	0.73	10.61
Non-Hodgkin Lymphoma	23,852	39	1.33	0.95	1.82	2,731	1	0.29	0.00	1.61	2,154	1	0.6	0.01	3.34
Leukemia	16,110	14	0.91	0.50	1.53	1,545	0	0	NA	NA	1,485	2	3.68	0.41	13.29

Appendix 2c. Relationship between prior primary cancers and subsequent pancreatic cancer (female, age <= 64 years)															
Age <=64 yrs, 12 month latency period	White					Black					Asian				
Female	Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI	
All Sites	479,307	559	1.10#	1.01	1.20	60,871	95	1.27#	1.03	1.55	61,382	53	1.24	0.93	1.62
Oral Cavity and Pharynx	6,687	9	1.35	0.62	2.56	1,052	3	2.69	0.54	7.86	1,250	1	1.35	0.02	7.51
Stomach	2,388	1	0.61	0.01	3.39	622	0	0	NA	NA	923	1	1.86	0.02	10.35
Colon excluding Rectum	19,171	32	1.27	0.87	1.79	4,304	9	1.35	0.62	2.56	3,232	5	1.71	0.55	3.99
Cecum	3,629	8	1.66	0.71	3.27	1,018	1	0.63	0.01	3.51	359	0	0	NA	NA
Ascending Colon	2,520	4	1.17	0.31	3.00	730	5	4.15#	1.34	9.68	361	0	0	NA	NA
Hepatic Flexure	732	0	0	NA	NA	170	2	6.91	0.78	24.95	128	1	7.09	0.09	39.45
Transverse Colon	1,410	3	1.47	0.30	4.30	359	0	0	NA	NA	241	0	0	NA	NA
Sigmoid Colon	7,557	8	0.78	0.34	1.54	1,211	1	0.49	0.01	2.73	1,562	3	2.03	0.41	5.93
Rectum	7,510	5	0.61	0.20	1.42	1,295	2	1.16	0.13	4.19	1,414	0	0	NA	NA
Gallbladder	553	1	2.7	0.04	15.02	97	2	33.10#	3.72	119.51	88	1	31.43	0.41	174.87
Intrahep and Extrahep Bile Ducts, and Other Biliary	763	3	8.02#	1.61	23.43	99	0	0	NA	NA	183	1	15.33	0.20	85.29
Lung and Bronchus	20,791	26	1.68#	1.10	2.46	3,505	4	1.32	0.36	3.38	2,197	2	2	0.22	7.22
Melanoma of the Skin	32,113	27	1.03	0.68	1.50	159	0	0	NA	NA	321	1	5.82	0.08	32.38
Female Breast	195631	270	1.07	0.95	1.21	26308	51	1.37#	1.02	1.80	26841	22	1.01	0.63	1.53
Corpus Uteri	36294	56	1.03	0.78	1.34	3197	5	1.01	0.33	2.36	5166	5	1.2	0.39	2.80
Ovary	17595	23	1.75#	1.11	2.63	1569	1	0.74	0.01	4.12	2543	2	1.57	0.18	5.67
Prostate	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA
Urinary Bladder	6,384	9	0.84	0.38	1.59	474	2	2.37	0.27	8.56	349	2	5.26	0.59	18.99
Kidney and Renal Pelvis	9,332	11	1.18	0.59	2.11	1,517	1	0.52	0.01	2.89	775	1	1.92	0.03	10.68
Thyroid	31,964	24	1.34	0.86	1.99	2456	1	0.46	0.01	2.56	5,270	2	0.84	0.09	3.03
Non-Hodgkin Lymphoma	16,680	13	0.74	0.39	1.27	2,101	3	1.2	0.24	3.51	1,853	3	2.25	0.45	6.57
Leukemia	10,392	9	1.4	0.64	2.66	1,103	1	1.33	0.02	7.40	1,168	0	0	NA	NA

Appendix 3a. Relationship between prior primary cancers and subsequent pancreatic cancer (male and female, age >= 65 years)															
Age >=65 yrs, 12 month latency period	White					Black					Asian				
Male and female	Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI	
All Sites	844,257	2,725	0.98	0.94	1.02	81,020	329	1.08	0.97	1.20	79,398	240	1.15#	1.01	1.31
Oral Cavity and Pharynx	15,892	46	1.07	0.78	1.43	1,108	6	1.94	0.71	4.22	1,564	0	0	NA	NA
Stomach	9,099	33	1.80#	1.24	2.53	1,382	5	1.46	0.47	3.41	3,380	11	1.55	0.77	2.77
Colon excluding Rectum	79,761	280	1.07	0.95	1.20	8,262	34	1.08	0.75	1.51	9,149	29	1.14	0.76	1.64
Cecum	20,431	66	1.02	0.79	1.30	2,162	7	0.86	0.34	1.77	1495	3	0.73	0.15	2.13
Ascending Colon	15,105	71	1.49#	1.16	1.88	1,583	9	1.52	0.69	2.89	1,561	2	0.48	0.05	1.73
Hepatic Flexure	4,527	25	1.68#	1.09	2.48	432	3	1.88	0.38	5.49	481	4	3.05	0.82	7.81
Transverse Colon	7,063	21	0.94	0.58	1.44	735	4	1.44	0.39	3.69	796	3	1.32	0.27	3.86
Sigmoid Colon	23,136	74	0.9	0.71	1.13	2,055	7	0.84	0.34	1.73	3,593	14	1.35	0.74	2.27
Rectum	18,556	51	0.89	0.66	1.17	1,544	7	1.33	0.53	2.74	2,615	5	0.74	0.24	1.73
Gallbladder	1339	5	2.24	0.72	5.23	110	2	9.62#	1.08	34.73	213	1	2.37	0.03	13.19
Intrahep and Extrahep Bile Ducts, and Other Biliary	2,537	10	2.81#	1.35	5.17	162	0	0	NA	NA	584	2	3.14	0.35	11.34
Lung and Bronchus	66,510	107	1.07	0.88	1.29	6,899	7	0.6	0.24	1.24	7,265	7	0.77	0.31	1.59
Melanoma of the Skin	31,085	101	0.97	0.79	1.18	181	0	0	NA	NA	299	0	0	NA	NA
Female Breast	132650	452	0.98	0.89	1.07	11162	42	0.89	0.64	1.20	10698	52	1.63#	1.22	2.14
Corpus Uteri	27212	75	0.80#	0.63	1.00	2134	10	1.42	0.68	2.61	1731	7	1.52	0.61	3.13
Ovary	10529	17	0.87	0.51	1.39	715	1	0.58	0.01	3.23	761	0	0	NA	NA
Prostate	229,191	949	0.94	0.88	1.00	30,875	166	1.15	0.98	1.34	20,866	91	1.26#	1.01	1.55
Urinary Bladder	55,684	209	1.09	0.95	1.25	2,438	14	1.6	0.87	2.68	3,437	6	0.6	0.22	1.31
Kidney and Renal Pelvis	19,975	63	1.09	0.84	1.39	1,941	6	0.92	0.34	2.00	1,714	5	1.3	0.42	3.03
Thyroid	6,646	19	0.92	0.55	1.44	495	0	0	NA	NA	1,195	1	0.32	0.00	1.78
Non-Hodgkin Lymphoma	34,819	96	0.99	0.80	1.21	1,690	3	0.54	0.11	1.58	3,088	5	0.68	0.22	1.59
Leukemia	19,677	41	0.8	0.57	1.09	1,258	1	0.29	0.00	1.61	908	1	0.63	0.01	3.51

Appendix 3b. Relationship between prior primary cancers and subsequent pancreatic cancer (male, age >= 65 years)															
Age >=65 yrs, 12 month latency period	White					Black					Asian				
Male	Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI	
All Sites	471,618	1,688	0.99	0.94	1.04	47,947	230	1.21#	1.06	1.38	45,593	138	1.09	0.92	1.29
Oral Cavity and Pharynx	9,920	36	1.29	0.90	1.79	704	3	1.73	0.35	5.05	964	0	0	NA	NA
Stomach	5,386	24	2.19#	1.40	3.26	669	2	1.29	0.14	4.66	1,965	7	1.69	0.68	3.48
Colon excluding Rectum	36,535	151	1.18	1.00	1.38	3,348	13	1.07	0.57	1.83	4,505	12	0.93	0.48	1.62
Cecum	8,208	32	1.15	0.79	1.62	803	1	0.35	0.00	1.95	610	1	0.58	0.01	3.23
Ascending Colon	6,391	40	1.87#	1.34	2.55	609	3	1.4	0.28	4.09	645	1	0.55	0.01	3.06
Hepatic Flexure	2,072	15	2.10#	1.17	3.46	175	2	3.09	0.35	11.16	230	2	3.18	0.36	11.48
Transverse Colon	3,037	12	1.16	0.60	2.03	283	2	2	0.22	7.22	385	2	1.75	0.20	6.32
Sigmoid Colon	12,027	42	0.92	0.66	1.24	900	3	0.87	0.17	2.54	1,966	5	0.85	0.27	1.98
Rectum	10,033	28	0.86	0.57	1.24	722	5	2.05	0.66	4.78	1,488	2	0.52	0.06	1.88
Gallbladder	310	2	4	0.45	14.44	27	0	0	NA	NA	71	0	0	NA	NA
Intrahep and Extrahep Bile Ducts, and Other Biliary	1,306	8	4.09#	1.76	8.06	68	0	0	NA	NA	292	1	3.44	0.04	19.14
Lung and Bronchus	32,615	52	1.03	0.77	1.35	3,581	7	1.2	0.48	2.47	4,089	6	1.16	0.42	2.52
Melanoma of the Skin	19,262	60	0.89	0.68	1.15	83	0	0	NA	NA	159	0	0	NA	NA
Female Breast	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA
Corpus Uteri	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA
Ovary	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA
Prostate	229,191	949	0.94	0.88	1.00	30,875	166	1.15	0.98	1.34	20,866	91	1.26#	1.01	1.55
Urinary Bladder	42,272	157	1.05	0.89	1.23	1,521	11	2.03#	1.01	3.63	2,582	3	0.4	0.08	1.17
Kidney and Renal Pelvis	11,738	39	1.09	0.77	1.49	997	4	1.21	0.33	3.10	1,022	3	1.28	0.26	3.74
Thyroid	2,002	7	1.01	0.40	2.08	111	0	0	NA	NA	304	0	0	NA	NA
Non-Hodgkin Lymphoma	16,786	52	1.07	0.80	1.40	742	3	1.31	0.26	3.83	1,582	3	0.8	0.16	2.34
Leukemia	11,062	25	0.84	0.54	1.24	613	1	0.65	0.01	3.62	541	0	0	NA	NA

Appendix 3c. Relationship between prior primary cancers and subsequent pancreatic cancer (female, age >= 65 years)															
Age >=65 yrs, 12 month latency period	White					Black					Asian				
Female	Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI		Persons	Observed	O/E	95% CI	
All Sites	372,639	1,037	0.96	0.90	1.02	33,073	99	0.87	0.71	1.06	33,805	102	1.25#	1.02	1.52
Oral Cavity and Pharynx	5,972	10	0.66	0.32	1.21	404	3	2.21	0.44	6.46	600	0	0	NA	NA
Stomach	3,713	9	1.21	0.55	2.30	713	3	1.6	0.32	4.67	1,415	4	1.35	0.36	3.46
Colon excluding Rectum	43,226	129	0.98	0.82	1.16	4,914	21	1.09	0.67	1.67	4,644	17	1.36	0.79	2.18
Cecum	12,223	34	0.93	0.64	1.30	1,359	6	1.14	0.42	2.48	885	2	0.84	0.09	3.03
Ascending Colon	8,714	31	1.18	0.80	1.67	974	6	1.59	0.58	3.46	916	1	0.42	0.01	2.34
Hepatic Flexure	2,455	10	1.3	0.62	2.39	257	1	1.05	0.01	5.84	251	2	2.94	0.33	10.61
Transverse Colon	4,026	9	0.75	0.34	1.42	452	2	1.12	0.13	4.04	411	1	0.88	0.01	4.90
Sigmoid Colon	11,109	32	0.89	0.61	1.26	1,155	4	0.81	0.22	2.07	1,627	9	2	0.91	3.80
Rectum	8,523	23	0.93	0.59	1.40	822	2	0.71	0.08	2.56	1,127	3	1.03	0.21	3.01
Gallbladder	1029	3	1.73	0.35	5.05	83	2	13.06#	1.47	47.15	142	1	3.56	0.05	19.81
Intrahep and Extrahep Bile Ducts, and Other Biliary	1,231	2	1.25	0.14	4.51	94	0	0	NA	NA	292	1	2.88	0.04	16.02
Lung and Bronchus	33,895	55	1.1	0.83	1.43	3,318	0	0.00#	NA	NA	3,176	1	0.25	0.00	1.39
Melanoma of the Skin	11,823	41	1.1	0.79	1.49	98	0	0	NA	NA	140	0	0	NA	NA
Female Breast	132650	452	0.98	0.89	1.07	11162	42	0.89	0.64	1.20	10698	52	1.63#	1.22	2.14
Corpus Uteri	27212	75	0.80#	0.63	1.00	2134	10	1.42	0.68	2.61	1731	7	1.52	0.61	3.13
Ovary	10529	17	0.87	0.51	1.39	715	1	0.58	0.01	3.23	761	0	0	NA	NA
Prostate	0	0	0	NA	NA	0	0	0	NA	NA	0	0	0	NA	NA
Urinary Bladder	13,412	52	1.25	0.93	1.64	917	3	0.91	0.18	2.66	855	3	1.25	0.25	3.65
Kidney and Renal Pelvis	8,237	24	1.09	0.70	1.62	944	2	0.62	0.07	2.24	692	2	1.32	0.15	4.77
Thyroid	4,644	12	0.88	0.45	1.54	384	0	0	NA	NA	891	1	0.42	0.01	2.34
Non-Hodgkin Lymphoma	18,033	44	0.91	0.66	1.22	948	0	0	NA	NA	1,506	2	0.56	0.06	2.02
Leukemia	8,615	16	0.75	0.43	1.22	645	0	0	NA	NA	367	1	1.68	0.02	9.35

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CHAPTER 2: ASSOCIATION OF PANCREATIC CANCER AND PRIOR NON-CANCER CHRONIC DISEASES

INTRODUCTION

There are a number of prominent chronic diseases that are more common in western countries than they are in traditional non-Western cultures. The underlying motivation of this thesis is to explore whether pancreatic cancer is associated with some of these diseases and to use such associations (if found) to develop hypotheses about the etiology of pancreatic cancer. In Chapter 1 we explored associations of pancreatic cancer with a number of cancers that are more common in the West, and in this Chapter we explore associations with non-cancer chronic diseases that are more common in Western than in non-Western cultures. Based on the Health and Retirement Study (HRS) in 2008, about 87% of older people in US have one or more chronic diseases such as hypertension, heart disease, stroke, diabetes, cancer, chronic lung disease, and/or arthritis; the prevalence of above diseases are: hypertension (65.0%), heart disease (31.6%), stroke (9.2%), diabetes (22.7%), chronic obstructive pulmonary disease (COPD, 12.3%), and arthritis (68.8%). [1] Studies show "unhealthy" Western lifestyles and physical attributes are associated with a number of these diseases including coronary heart disease, stroke, diabetes, cholecystitis, gallstones, appendicitis, diverticular disease, COPD, and probably asthma. [2-14] A recent meta-analysis found that obesity comorbidities include type II diabetes, all major cancer except esophageal and prostate, cardiovascular diseases, asthma, gallbladder disease, osteoarthritis, and chronic back

pain, [15] which implies non-cancer chronic disease and cancer such as pancreatic cancer might share some risk factors associated with Western lifestyle.

Coronary heart disease (CHD) is the leading cause of death in Western countries. The CHD death rate peaked the West in the 1960s, and fell 66% in men and 67% in women from 1980 to 2009. A direct measure of national incidence is not available; however, community surveillance, cohort studies, and health care delivery system data provide some incidence results, which although varied geographically, showed evidence that CHD incidence may have declined in US. [16] Incidence of new coronary disease has fallen much more slowly, than mortality which may be partly because of the increased sensitivity of enzyme diagnosis of MI. Community surveillance in Rochester, Minnesota showed the age and sex adjusted incidence rate of CHD including angina pectoris, MI (Myocardial infarction), and sudden death fell from 589 per 100,000 during 1950-1954 to 559 per 100,000 during 1979-1982. [17] A study based on National Health and Nutrition Examination Survey showed the age-adjusted incidence of CHD decreased from 133.3 per 1,000 in the period of 1971 to 1984 to 113.5 per 1,000 in the period of 1984 to1992. [18] The incidence decreased significantly in black men (-18.5%), white men (-14.6%), and white women (-11.4%).Recent study based on administrative data from Kaiser Permanent indicated the age- and sex-adjusted CHD incidence rate decreased from 274 per 100,000 in 1999 to 208 per 100,000 in 2008. The rate of STEMI (ST segment elevation myocardial infarction) declined significantly from 133 to 50, but not the rate of NSTEMI (Non–ST-segment elevation myocardial infarction). [19] In general, the secular incidence trends of CHD and pancreatic cancer seem parallel with both peaking about

1970 and falling slowly thereafter. Among the major changes in risk factors for CHD, cigarette smoking fell from 42.4% in 1965 to 18.1% in 2011, [20] and secondhand smoking exposure for nonsmokers also declined. [21] Smoking is the strongest environmental risk factor for pancreatic cancer. [22] Another major change is mean serum cholesterol, which was 222 mg/dL during 1960-1962, and fell to 196 mg/dL during 2007-2010. [23] Although studies suggest serum cholesterol might be associated with pancreatic cancer, the level of evidence is much weaker than it is for coronary heart disease.[24]

Despite a remarkable decline in stroke incidence and mortality of more than 50% in the U.S. from the 1950's to today [25] [26] , stroke remains a major cause of morbidity in elderly Americans and is the fourth leading cause of death. The major risk factor change causing the reduction in stroke is control of hypertension, [25] which started in 1950s. Reduction in smoking and control of dyslipidemia is believed to have contributed as well, particularly to prevention of ischemic stroke which accounts for about 80% of stroke incidence and 50% of stroke mortality. [26] There are few publications on the relationship between hypertension and pancreatic cancer, with both positive and negative associations being reported. [27] The linkage study of Hypertension Registry and Cancer Registry in Finland by Lindgren et al showed SIR (standardized incidence ratio) of 1.26 with 95% CI 1.02-1.54 for pancreatic cancer in the hypertensive population compared with with general population. [27] However, a case-cohort study reported hazard ratio of 0.66, 95% CI 0.49-0.90 in hypertensive population. [28]

COPD (chronic obstructive pulmonary disease) including chronic bronchitis and emphysema has declined less through the years than did stroke, and as a result, has

become the number three leading cause of death in US. [29-31] Smoking is a common risk factor for COPD and pancreatic cancer. Between 1999 and 2011, chronic bronchitis shows decreasing trend, but emphysema has increased some, so that the overall trend of prevalence of COPD looks stable, [31] which is similar to pancreatic cancer.

Diverticulitis is one of most prevalent diseases in US especially among older people. Hospital admissions in US increased 26% from 1998 to 2005, particularly in young adults aged 18-44 years (82% increase) and those aged 45-74 years (36%).[32] There is also geographic variation from 61.8 to 75.5 per 100,000, from lowest West (50.4 per 100,000) to highest Northeast (77.7 per 100,000). [33] We could not find publications on association between diverticulitis and pancreatic cancer. The incidence of appendicitis increased in industrialized countries until middle of last century, [34] no statistically significant association between appendectomy or appendicitis and pancreatic cancer was found based on the meta-analysis by Olson SH. [35]

Many studies shows evidence of negative association between allergy and pancreatic cancer, especially hay fever or respiratory allergies, but not asthma, and ranged between 0.3 (95% CI 0.1-1.4) to 0.85 (95% CI 0.77-0.95). The mechanism is not clear; perhaps an increased level of immune surveillance in the body may protect against pancreatic cancer. [35]

APPROACH

The SEER-Medicare database provides an efficient way to assess the frequency of non-cancerous chronic diseases in a large representative sample of US persons with pancreatic cancer. This resource was created by the National Cancer Institute and CMS

(Centers for Medicare & Medicaid Services) by matching the SEER database to the Medicare database.[36] It provides a unique opportunity to investigate pancreatic cancer among the large elderly population on demographics and medical history (including outpatient visits and hospitalization) by medical claims since 1991. With the expansion of SEER in 2001 through the addition of four states (California, Louisiana, Kentucky, and New Jersey), SEER increased it's coverage to 26% of the US population. The SEER-Medicare database has more than 3,000 pancreatic cancer cases each year from 2000 to 2009 and about 1,500 each year from 1991 to 1999.[37]

In this chapter, using SEER-Medicare we explore the association of pancreatic cancer with non-cancer chronic diseases that are more frequent in Western societies than in developing countries. These include diseases such as coronary heart disease, ischemic stroke, hyperlipidemia, hypertension, diabetes, COPD, pancreatitis, diverticulitis, and appendicitis. It is hoped that these associations will provide clues as to what aspects of Western lifestyle contribute to the excess pancreatic cancer seen in market economies.

METHODS

We used SEER-Medicare data for the period 1991 to 2011 to conduct a case-control study. Medicare beneficiaries (65-89 years of age) with pancreatic cancer registered in SEER during 1991-2011 were the source of cases, and a 5% random sample of beneficiaries without cancer was used as the source of controls.

Data Source

We used SEER-Medicare data 1991-2011 for our study. SEER cancer registries include SEER incidence and population data associated by age, sex, race, year of diagnosis, and geographic areas. [38] SEER coverage includes 26 percent of African Americans, 38 percent of Hispanics, 44 percent of American Indians and Alaska Natives, 50 percent of Asians, and 67 percent of Hawaiian/Pacific Islanders. [39] The SEER-Medicare data is a large population-based database linking SEER registries data from National Cancer Institute (NCI) and Medicare claim data from Centers for Medicare and Medicaid Serves (CMS).[36] The SEER cancer registries collects detail cancer information of patients in demographic, cancer location, pathological stage and grade, treatment, and cause of death; While Medicare data provides medical claims, and pharmacy claims (since year 2006) for covered health care services from the time of a person's Medicare eligibility until death. The SEER-Medicare data also includes a random 5% sample of non-cancer Medicare beneficiaries residing in the SEER areas. Medicare beneficiaries can get their Medicare benefits through Original Medicare (traditional fee-for-service plan), or a Medicare Advantage Plan (like HMO, Health Maintenance Organization, or PPO, Preferred Provider Organization). In the traditional fee-for-service plan, the government pays for Medicare benefits and keeps claim data. In Medicare Advantage Plans, Medicare pays these companies to cover Medicare benefits and doesn't have claim data. Therefore we will select beneficiaries enrolled in the traditional fee-for-service plan, which includes Part A plan (hospital insurance) and Part B plan (medical insurance). Data on these beneficiaries is organized in six major files:

1. Patient Entitlement and Diagnosis Summary File (PEDSF) 1973-2011, including one record per person for patients in the SEER database who have been matched with Medicare enrollment records.

Information utilized	Study Variables
Socio-demographics variables, Medicare information	Medicare birth month and year, SEER age at diagnosis, SEER diagnosis month and year; sex, race, ethnicity; linkage year, SEER registry code, Reason for Medicare entitlement, entitlement Indicators, number of months covered for Part A, B, D and HMO , dual eligibility status
Survival time, cause of death	Medicare death month, Medicare death day, Medicare death year, cause of death; SEER month and year of death, survival time

2. *Summarized Denominator File (SUMDENOM), 1991-2011, including non-cancer persons identified from a random 5% sample of Medicare beneficiaries residing in the SEER areas.*

Information utilized	Study Variables
Socio-demographics variables, Medicare information	Medicare birth month and year, sex, race, ethnicity, linkage year, registry code, reason for Medicare entitlement, entitlement Indicators, number of months covered for Part A, B, D and HMO , dual eligibility status
Survival time	Medicare death month, Medicare death day, Medicare death year

3. *Medicare Provider Analysis and Review (MEDPAR) File 1991-2013, including Part A short stay, long stay of inpatient care, and skilled nursing facility bills for each calendar year*

Information utilized	Study Variables
Socio-demographics variables,	Medicare status

Medicare information	
Survival time	Medicare death month, Medicare death day, Medicare death year,
Comorbid conditions, treatments, screening	Admission date month, day, and year; Discharge date month, day, and year; Number of days for hospital stay, Diagnosis and procedure codes (ICD-9-CM), Types of services provided (using HCPCS codes)

4. *Carrier Claims File 1991-2013, including Part B claims submitted from physicians and other non-institutional providers*

Information utilized	Study Variables
Socio-demographics variables, Medicare information	Type of claim
Comorbid conditions , Treatments	Service dates (mmddyyyy), type of services provided (using HCPCS codes), number of services done, diagnosis and procedure codes (ICD-9-CM); diagnosis code count

5. *Outpatient Claims File 1991-2013, including Part B claims submitted from institutional outpatient providers*

Information utilized	Study Variables
Socio-demographics variables, Medicare information	Type of claim
Comorbid conditions, Treatments	Service dates (mmddyyyy), types of services provided (HCPCS codes) and revenue centers, diagnosis codes and procedure codes (ICD-9 CM)

6. *Part D Event File 2007-2013, including Part D prescription event information*

Information utilized	Study Variables
Prescription medications	Prescription service date, national drug code, quantity dispensed, days supplied; dosage form, dose strength, drug name (brand and generic)

Cases

Cases included all patients in the SEER-Medicare database diagnosed with pancreatic cancer at ages 65-89 during the years 1991 through 2011 who were continuously enrolled in Part A and Part B of Medicare for at least two calendar years before the year of diagnosis of pancreatic cancer. For purposes of matching length of follow-up, the year of diagnosis was called the "index year". Potential cases not enrolled for at least two years prior to the index year were excluded. Pancreatic cancer was defined based on *International Classification of Diseases for Oncology,* Third Edition (ICD-O-3), the primary site code includes 250-254 and 257-259, and the histologic ttype (ICD-O-3) includes 8010-8012,8015,8020-8022,8140-8141,8143,8147,8210-8211,8230-8231,8260-8263,8440,8450,8452-8453,8470-8471,8480-8481,8490,8503-8504,8507-8508,8510,8514,8521,8560,8562,8570-8576.

Controls

The controls were selected from a 5% random sample of Medicare beneficiaries who resided in the same SEER registry area and were free of cancer as evidenced by not being registered in SEER. For each person in the 5% sample a randomly selected year with continuous enrollment of both Part A and B was assigned as the index year; those continuously enrolled in both Parts A and B of Medicare for at least two calendar years before the randomly assigned index year were included, and those not enrolled for at least two calendar year before the index year, as well as those not in the 65-89 year age range in the index year, were excluded.

In a second step a subset of controls was frequency matched in a 5:1 ratio on age attained in the index year (five year groups), and length of time from the beginning of continuous enrollment to the index date (five year groups), to create a set of controls who were closely comparable to the cases on these variables.

Prior Occurrence of Non-cancer Diseases

For cases and controls we searched the Medicare claims database for diagnoses of non-cancer chronic diseases of interest (listed in Appendix A) that occurred between the start of continuous enrollment and a year before the index date. Some of the important diseases were: coronary heart disease (ICD 9 code of 410.xx, 413.xx), stroke (ICD 9 code of 431.xx, 433.x1, 434.x1), hyperlipidemia (ICD 9 code of 272.4), and other comorbidities diverticulitis (ICD 9 code of 562.xx), appendicitis (ICD 9 code of 540.xx), pancreatitis (ICD 9 code of 577.xx), COPD (ICD 9 code of 490.xx-492.xx, 494.xx, 496.xx), asthma (ICD 9 code of 493.xx). The medical claim of diagnosis based on ICD 9 codes are from inpatient claim (MEDPAR), and outpatient claim (Carrier Claims File or NCH and Outpatient Claims File). At least one inpatient claim or two separate outpatient claims (with interval >= 1 month) with primary diagnosis code were required for identifying the chronic diseases of interest.

Statistical analysis and Human Subjects Approval

A case-control analysis was performed. We applied logistic regression models to measure strength of association between non-cancer chronic diseases and pancreatic cancer. Odds ratios are shown with and without adjustment for other covariates or confounders (age, gender, race, length of enrollment, and comorbidities).

The study protocol was reviewed and approved by the National Cancer Institute and by the Independent Review Board of Rutgers University.

RESULTS

During 1991-2011 the total number of 65-89 year-old Medicare beneficiaries registered in SEER with pancreatic cancer was 100,407; among whom 50,161 were diagnosed as malignancy with positive histology in the listed histologic code; and 28,375 were without ESRD (End Stage Renal Disease), enrolled for at least two calendar years with traditional fee-for-service Medicare plan before the index year when pancreatic cancer was diagnosed, and age 65-89 years at diagnosis of pancreatic cancer. The total number of 5% randomly selected non-cancer beneficiaries during 199 to 2011 was 826,833, and 425,709 were without ESRD (End Stage Renal Disease), enrolled for at least two calendar years with traditional fee-for-service Medicare plan before the index year randomly selected from the continuous enrollment years, and age 65-89 years at the index year. We selected cases and controls with at least two continuous enrollment years for traditional fee-for-service Medicare with both Part A and Part B plan before the index year.

To reduce confounding by the differences in age and length of continuous enrollment (exposure time), a reduced set of controls was created that was limited to

five times the number of cases and was frequency matched to cases on age and length of enrollment (five year groups). As expected, this resulted in very similar distributions of these two variables between cases and this smaller set of controls as shown in Table 1 and Table 2. Before matching, as shown in Table 1 this resulted in total of 28,375 eligible cases with a mean age of 76.7 years and 425,709 eligible controls with a mean age of 73.4 years. There was also an important difference in average years of observation which was 8.55 years in cases and 10.19 years in controls (Table 2).

As Table 3 shows, the age distribution in case and control was similar after matching, but the percentage of females was lower in cases than in controls (51.64% vs. 59.58%), Most Medicare beneficiaries in our study population were White and the percentages of Whites in case and control groups was similar (82.96% of cases, 81.32% of controls). The percentage of Blacks was higher in case than in control groups (cases 9.68%, controls 7.65%). Hispanic, Asian, Native American, and other ethnicities each had small samples and if collapsed into one group, the combined group had lower percentage in cases than in controls (7.20% vs. 10.61%).

Associations with Coronary Disease and Its Risk Factors

There was a substantial association between prior coronary heart disease (CHD) and pancreatic cancer. Among cases 11.46% had prior CHD as compared with only 8.18% of the controls (Table 3), giving a crude odds ratio of 1.45 (Table 4a) for pancreatic cancer. Adjustment for age, gender, race, and length of enrollment changed the odds ratio only slightly to 1.44 (Table 4b). However, adding three important coronary risk factors (hyperlipidemia, hypertension, and diabetes) to the model

substantially reduced this odds ratio to 1.07 (Table 5). Smoking was not available for analysis but an association between COPD and pancreatic cancer suggests that it too might play an explanatory role in the apparent association of CHD with pancreatic cancer. Addition of COPD to the model had little effect on the adjusted CHD odds ratio (Table 5).

Associations with Non-malignant Gastrointestinal Diseases

The well known association between pancreatic cancer and pancreatitis was very strong in these data with a prevalence of such history in 5.1 % of the cancer cases vs. 1.0% of controls. Strong associations with liver disease, including alcoholic hepatitis and cirrhosis were also seen (5.0% vs. 2.6%) and are consistent with the role of alcohol in the etiology of pancreatitis (Table 3). Adjustments for age, gender, race, and length of enrollment did not attenuate these findings (Table 4b). We did sensitivity analysis on association between pancreatitis and pancreatic cancer as well as between liver diseases and pancreatic cancer by excluding diagnosis records for different interval lengths before index year. For pancreatitis the adjusted odds ratios decreased dramatically from index year (30.03), one year before index year (5.37), and three years before index year (3.20), and for liver diseases the adjusted odds ratios were 6.29, 2.07, 1.80 respectively (Table 6)

Appendicitis, diverticulitis and Crohn's disease have all been cited as conditions that are uncommon among poor persons in non-Western countries, and it is of interest that pancreatic cancer was significantly associated with each of these conditions with adjusted odds ratios of 1.60, 2.30, and 1.80, respectively (Table 4b).

Autoimmune and allergic conditions

The hygiene hypothesis that has been widely considered as a possible explanation for allergic rhinitis and asthma in Western countries provides a rationale for considering these conditions as possible "Western" diseases. The allergy and autoimmune diseases that we were able to tabulate were at modestly higher prevalence in cases compared with controls: asthma (6.00% vs. 4.53%), allergic rhinitis (7.58% vs. 5.62%), rheumatoid arthritis (2.72% vs. 2.08%). and the resulting odds ratios were mostly in the 1.2–1.4. While not impressive in magnitude these asociations were statistically significant. Systematic Lupus Erythematosus (0.26% vs. 0.26%) had no association. Crohn's disease (0.44% vs. 0.26%) had a stronger association as mentioned above.

Neurological Diseases

A somewhat surprising finding from this exploratory analysis was the apparently low rate of pancreatic cancer in subjects with a history of serious neurological diseases, specifically, Parkinson's Disease (0.73% vs. 1.30%), Alzheimer's Disease (0.77% vs. 1.71%), and unspecified dementia (0.98% vs. 2.20%) (Table 3). These comparisons translate into substantially protective odds ratios: 0.52, 0.43, and 0.41, respectively.

DISCUSSION

Our study showed that pancreatic cancer is strongly age-related and that women had lower risk of pancreatic cancer compared with men, which is consistent with other publications.[22,40] In addition, our findings confirmed Blacks were at higher risk of

pancreatic cancer than Whites, while other races including Asian, Hispanic, Native American, and others had lower risk of pancreatic cancer. [29,22]

We found many chronic diseases that are health problems in Western countries to be positively associated with pancreatic cancer. In general these associations persisted after adjustment for age, gender, race, and length of enrollment. In the case of coronary heart disease we found that adjustment for its well known risk factors substantially attenuated the association, implying that these risk factors, or some correlates or combination of them is associated with pancreatic cancer. CHD and pancreatic cancer have had parallel in trends in incidence since 1970[16-19], although the decline in CHD mortality has been larger. They share smoking, heavy alcohol drinking, obesity, and diabetes as common risk factors. [22,41-44,45-48] but differ in that modest alcohol intake is protective for CHD incidence. Of these risk factors only smoking has shown a declining trend.. [20,21] The protective effect of modest alcohol consumption for CHD might contribute to its steeper decline. [49,50] Other risk factors such as high cholesterol and hypertension are important for CHD, [51] but their associations with pancreatic cancer are not so clear.[24]

Stroke incidence and prevalence is dominated by ischemic cases which are mostly caused by atherosclerosis and share some risk factors with CHD. Stroke had a crude OR of 1.08 for pancreatic cancer which also was largely attenuated by adjustment for risk factors (Table 6). Stroke incidence and mortality have declined remarkably since the 1950's in the U.S. and in many other countries. Better control of blood pressure is believed to be the dominant cause of this decline, but reduction in serum cholesterol

and smoking and availability of anticoagulants could also be contributors.[26,41] Although other studies find increased risk of stroke *after* diagnosis of pancreatic cancer, [52] our analysis focused on the years before the diagnosis of pancreatic cancer, thus eliminating the possibility that the cancer somehow contributed to the strokes. Since pancreatic cancer is a lethal disease with short survival time, study of the incidence of other diseases after pancreatic cancer is difficult. [29]

Both crude and adjusted odds ratios of hyperlipidemia for pancreatic cancer have been reported by others to be positive and statistically significant. In a meta-analysis Wang et al. showed significant association between high serum cholesterol and pancreatic cancer (OR: 1.275 (95% CI: 1.058-1.537) in studies based on North America, but not in Europe OR: 1.149 (95% CI: 0.863-1.531). [24,53] Statin use, a medication that is widely used to lower serum cholesterol seemed reduce 30% risk of pancreatic cancer in men, but not in women. [54,55] We found the association between hypertension and pancreatic cancer was also statistically positive both in crude and adjusted OR, which was consistent with Stocks et al. reported 10-mmHg increments in blood pressure in women was associated 27% increased risk of pancreatic cancer (HR: 1.27, 95% CI: 1.09-1.48), but null or even negative association between hypertension and pancreatic cancer have also been reported. [56-58]

The crude OR for COPD was 1.49 and was unaffected by demographic adjustments (Table 4b). COPD is a common comorbidity in patients with pancreatic cancer, [59] but we could not find a publication on COPD as a risk factor for pancreatic cancer. Smoking is a common risk factor,[22,60] but is much more strongly related to

COPD. We found diabetes was associated with pancreatic cancer with crude OR of 1.84 and adjusted OR of 1.89, which was consistent with most findings in recent publications, although there were controversies about whether diabetes is an antecedent or consequence of early pancreatic cancer. [46,47,61,62] It seems long-term diabetes (> 2 years before diagnosis of pancreatic cancer) is more likely a risk factor while new-onset diabetes (<= 2 years before diagnosis of pancreatic cancer) is more likely an early sign of pancreatic cancer. [63-65] Our sensitivity study showed recent record of diagnosis of diabetes had greater OR of 2.08 than the OR of 1.66 in diagnosis of diabetes recorded three years before index year (Table 6).

Liver diseases including alcoholic hepatitis, fatty liver, liver necrosis, liver abscess, and liver cirrhosis were strongly associated with pancreatic cancer, we had crude OR of 1.97 and adjusted OR of 2.07. Pancreatitis including acute pancreatitis and chronic pancreatitis had very strong association with pancreatic cancer, and we found crude OR of 5.26, and adjusted OR of 5.37. In addition to smoking, heavy alcohol drinking, and obesity, which are risk factors for both malignant and non-malignant pancreatic disease, the inflammatory and immune environment of pancreatitis might be related to metaplasia of acinar cells. [66-72] The very high risk of pancreatic cancer associated with pancreatitis decreased with longer duration of follow-up, which suggested that recent pancreatitis might be an early sign of pancreatic cancer.[67] Interestingly diverticulitis had crude OR of 1.89 and adjusted OR of 2.30. Both diverticulitis and pancreatic cancer share common risk factors such as smoking and obesity, diverticulitis is associated with less dietary fiber intake, intake of red meat and

alcohol, as well as diabetes, colon cancer, hyperlipidemia, and hypertension. [73-75] Appendicitis had crude OR of 1.58, Appendicitis occurs across a broad age range (including children) and has been considered a disease of Western life style, especially diet. Reduced dietary fiber intake has been suggested as a risk factor similar to diverticulitis,[76,77] while pancreatic cancer occurs mostly in elderly and seems not associated with dietary fiber. [22,40,78]

Atopic diseases, especially asthma and hay fever, are believed by many to be more common in more advantaged populations than among communities with little Western exposure. We found these diseases to be positively associated with pancreatic cancer. After adjustment for demographic variables, the odds ratios for asthma, allergic rhinitis, atopic dermatitis, and allergic urticaria ranged from 1.42 to 1.52 (Table 4b). The published associations between asthma and pancreatic cancer are not consistent. Some authors reported reduced risk of pancreatic cancer in asthma patients, especially if duration of asthma was long (>= 17 years), [79] but Olson et al. and Cotterchio et al. showed positive associations with asthma although there were negative association with other allergic diseases. [35,80]

We had data for three diseases believed to have an autoimmune pathogenesis, but found no consistent pattern of association with pancreatic cancer. After adjusting for demographic differences, rheumatoid arthritis (RA) had a statistically significant OR of 1.39, in association with pancreatic cancer, while the OR with systemic lupus erythematosus (SLE) was non-significant at 1.11, and for multiple sclerosis was 1.03, both association were not statistically significant. Other studies of a possible association

with rheumatoid arthritis showed minimal associations, [81] [82] and the association of pancreatic cancer with SLE found adjusted odds ratios of 1.13 (95% CI: 0.73-1.67) [83] and an SIR of 0.90 (95% CI: 0.43-1.65) in a multicenter international cohort study. [84] Our finding showed that multiple sclerosis had crude OR of 0.98, which was in contrast with Franks et al reported HR of 0.67. [85] Crohn's disease had a significant crude OR of 1.86.

Patients with neurodegenerative diseases had reduced risk of pancreatic cancer. After adjustment for age, gender, race, and length of enrollment Parkinson's disease had an adjusted OR of 0.52, Alzheimer disease had an OR of 0.43, and dementia had an OR of 0.41. Parkinson disease has an inverse association with smoking (OR: 0.56, 95% CI: 0.41-0.78) [86] which is the strongest environmental risk factor for pancreatic cancer, but the explanation for the protective effects of the dementias is unclear. Perhaps the most likely explanation is the omission of sophisticated diagnostic testing in patients with advanced dementia who go into physical decline. A physiological explanation might be related to the evidence in animal models that calorie restriction can reduce the incidence of some cancers.[87,88] Age is the major risk factors for both neurodegenerative disease and cancer, the shared glycolysis between cancer cells and synaptic plasticity of the brain were under selection pressure during aging process, increased glycolysis favored cancer cell growth while decreased glycolysis contributed to development of neurodegeneration. [89] In addition to changes of mitochondrial function, gene regulation of Pin1 and ubiquitin proteasome system might be also involved. [90]

We found synergistic interaction between diabetes and hyperlipidemia, liver disease, pancreatitis, as well as diverticulitis in the association with pancreatic cancer, which confirmed the findings of recent publications. [91-93]

CONCLUSION

Our study confirmed increased age, male gender, and Black race were important risk factors for pancreatic cancer. Other minority groups, whose lifestyles may differ from the dominant White pattern, had lower risk. Most of the chronic diseases that we tabulated are believed to be associated with Western lifestyles or related risk factors and several were associated with pancreatic cancer. These associations are only of moderate strength, but the multiplicity of associations suggests several aspects of Western lifestyles might contribute to pancreatic cancer risk. The associations with several coronary heart disease risk factors suggest the possibility that atherosclerosis in the coeliac and other arteries supplying pancreas might play a role. The strong association with pancreatitis emphasizes the importance of inflammation and the inflammatory potential of pancreatic exocrine secretions. Could the large amounts of protein and fat in Western diets trigger secretion of more proteases and lipases into the gastrointestinal tract and contribute not only to inflammation in the pancreas but also to appendicitis and diverticulitis downstream? Exploartion of such hypotheses might help us to better understand the etiology of pancreatic cancer. The intriguing findings with respect to diabetes will be presented in detail in chapter 3.

Tables and FIGURES

Figure 1. Flowchart of case and control selection

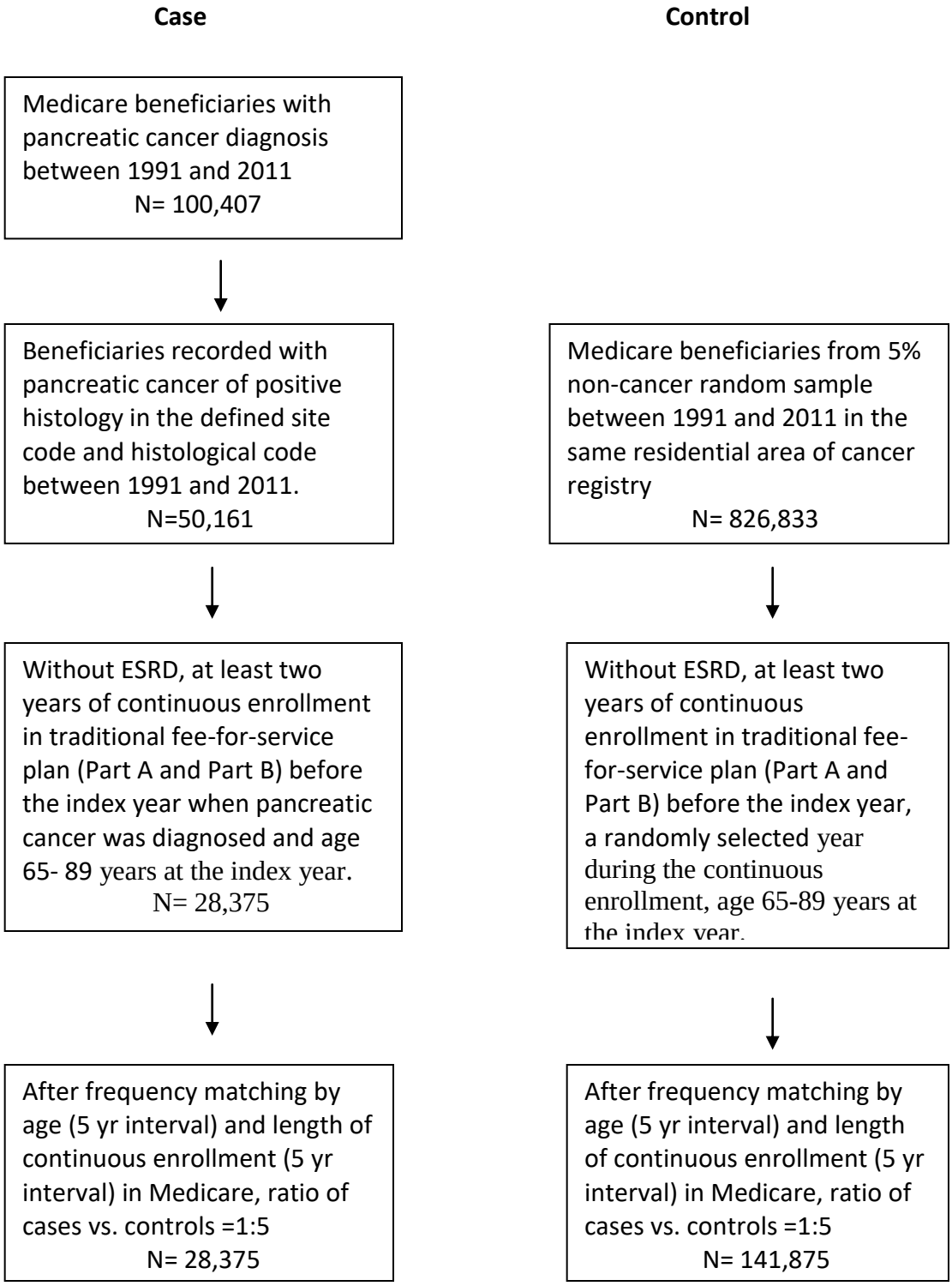

Table 1a. Age distribution among cases and controls

	Before matching			
	Case		Control	
Age (Year)	N	%	N	%
65-69	3,745	13.20	151,745	35.65
70-74	7,397	26.07	114,146	26.81
75-79	7,924	27.93	76,889	18.06
80-84	6,047	21.31	53,362	12.53
85-89	3,262	11.50	29,567	6.95
Total	28,375	100.00	425,709	100.00
	After matching			
	Case		Control	
65-69	3,745	13.20	18,725	13.20
70-74	7,397	26.07	36,985	26.07
75-79	7,924	27.93	39,620	27.93
80-84	6,047	21.31	30,235	21.31
85-89	3,262	11.50	16,310	11.50
Total	28,375	100.00	141,875	100.00

Note: for matching, cases and controls were grouped by both age (5 years interval) and length of enrollment (5 years interval), we included all cases of 28,375 for matching, and randomly selected controls from each age and enrollment group from control to match cases in the corresponding age and enrollment group from case at 5:1 ratio.

Table 1b. Average age in cases and controls

	N	Mean	STD	Median	Quartile Range	Minimum	Maximum
			Before matching				
Case	28,375	76.66	5.89	76.00	9.00	65.00	89.00
Control	425,709	73.42	6.22	72.00	10.00	65.00	89.00
			After matching				
Case	28,375	76.66	5.89	76.00	9.00	65.00	89.00
Control	141,875	76.34	6.12	76.00	10.00	65.00	89.00

See footnotes to Table 1a

Table 2a. Length of enrollment among cases and controls

	Before matching			
	Case		Control	
Length of Enrollment (Year)	N	%	N	%
1-4	9,295	32.76	121,546	28.55
5-9	7,837	27.62	94,538	22.21
10-14	7,524	26.52	102,925	24.18
15-19	3,370	11.88	65,508	15.39
>= 20	349	1.23	41,192	9.68
Total	28,375	100.00	425,709	100.00
	After matching			
	Case		Control	
1-4	9,295	32.76	46,475	32.76
5-9	7,837	27.62	39,185	27.62
10-14	7,524	26.52	37,620	26.52
15-19	3,370	11.88	16,850	11.88
>= 20	349	1.23	1,745	1.23
Total	28,375	100.00	141,875	100.00

See footnotes to Table 1a

Table 2b. Average length of enrollment in cases and controls

	N	Mean	STD	Median	Quartile Range	Minimum	Maximum
			Before matching				
Case	28,375	8.55	4.68	8.00	7.00	2.00	22.00
Control	425,709	10.19	6.05	9.00	10.00	2.00	23.00
			After matching				
Case	28,375	8.55	4.68	8.00	7.00	2.00	22.00
Control	141,875	8.73	4.87	8.00	7.00	2.00	23.00

See footnotes to Table 1a

Table 3. Demographic and non-cancer chronic disease characteristics

Demographic	Case		Control	
Age	76.66	5.89	76.34	6.12
Gender				
Female	14,653	51.64	84,534	59.58
Race				
White	23,540	82.96	115,379	81.32
Black	2,748	9.68	10,852	7.65
Others (sum of below races or ethnicity)	2,042	7.20	15,058	10.61
Hispanic	473	1.67	3,553	2.50
Asian	913	3.22	7,159	5.05
Native American	62	0.22	417	0.29
Other races	594	2.09	3,929	2.77
Non-cancer chronic diseases				
Coronary Heart Disease (CHD)	3,253	11.46	11,599	8.18
Stroke	1,998	7.04	9,303	6.56
Hyperlipidemia	11,130	39.22	35,464	25.00
Hypertension	14,433	50.87	50,643	35.70
COPD	5,054	17.81	18,047	12.72
Diabetes	7,243	25.53	22,264	15.69
Liver Diseases	1,404	4.95	3,651	2.57
Pancreatitis	1,434	5.05	1,422	1.00
Diverticulitis	3,517	12.39	9,869	6.96
Appendicitis	123	0.43	389	0.27
Asthma	1,702	6.00	6,431	4.53
Allergic rhinitis	2,151	7.58	7,968	5.62
Atopic dermatitis	422	1.49	1,474	1.04
Allergic urticaria	93	0.33	359	0.25
Rheumatoid Arthritis	771	2.72	2,953	2.08
Systematic Lupus Erythematosis	73	0.26	365	0.26
Multiple Sclerosis	34	0.12	174	0.12
Ulcerative colitis	202	0.71	618	0.44
Crohn's Disease	125	0.44	371	0.26
Parkinson's Disease	208	0.73	1,849	1.30
Alzheimer's Disease	219	0.77	2,428	1.71
Dementia	277	0.98	3,124	2.20

Note: based on 28,375 cases and 141,875 controls after matching of age and length of enrollment; The race “Others” included Hispanic, Asian, Native American, and other races as a combined race group to increase sample size for later analysis of odd ratios; non-cancer chronic diseases were defined by two outpatient primary diagnosis ICD 9

code (Appendix A) at least 30 days apart or one inpatient primary diagnosis one year before index year.

Table 4a. Crude odds ratio of demographic and diseases in association with pancreatic cancer

Characteristics	OR	95% CI	
Gender (Ref=Male)			
Female	0.72	0.71	0.74
Race (Ref=White)			
Black	1.24	1.19	1.30
Others (sum of below races or ethnicity)	0.74	0.68	0.81
Hispanic	0.65	0.59	0.72
Asian	0.63	0.58	0.67
Native American	0.73	0.56	0.95
Other races	0.66	0.63	0.70
Non-cancer chronic diseases			
Coronary Heart Disease (CHD)	1.45	1.40	1.52
Stroke	1.08	1.03	1.13
Hyperlipidemia	1.94	1.89	1.99
Hypertension	1.86	1.82	1.91
COPD	1.49	1.44	1.54
Diabetes	1.84	1.79	1.9
Liver Diseases	1.97	1.85	2.1
Pancreatitis	5.26	4.88	5.66
Diverticulitis	1.89	1.82	1.97
Appendicitis	1.58	1.29	1.94
Asthma	1.34	1.27	1.42
Allergic rhinitis	1.38	1.31	1.45
Atopic dermatitis	1.44	1.29	1.6
Allergic urticaria	1.44	1.29	1.6
Rheumatoid Arthritis	1.31	1.21	1.42
Systematic Lupus Erythematosis	1.00	0.78	1.29
Multiple Sclerosis	0.98	0.68	1.41
Ulcerative colitis	1.64	1.4	1.92
Crohn's Disease	1.69	1.38	2.07
Parkinson Disease	0.56	0.48	0.65
Alzheimer Disease	0.45	0.39	0.51
Dementia	0.44	0.39	0.5

Note: we take male as reference for the crude odd ratio of female, White as reference for other races, without the respective disease as reference for with the disease such as diabetes; also see footnotes to Table 3.

Table 4b. Odds ratio of diseases in association with pancreatic cancer adjusted by age, gender, race, and length of enrollment

Characteristics	OR	95% CI	
Coronary Heart Disease (CHD)	1.44	1.38	1.50
Stroke	1.04	0.99	1.10
Hyperlipidemia	2.27	2.20	2.33
Hypertension	2.08	2.02	2.13
COPD	1.51	1.45	1.56
Diabetes	1.89	1.83	1.95
Liver Diseases	2.07	1.94	2.20
Pancreatitis	5.37	4.98	5.78
Diverticulitis	2.30	2.21	2.39
Appendcitis	1.60	1.30	1.95
Asthma	1.42	1.34	1.50
Allergic rhinitis	1.48	1.41	1.56
Atopic dermatitis	1.52	1.36	1.69
Allergic urticaria	1.43	1.13	1.79
Rheumatoid Arthritis	1.39	1.28	1.51
Systematic Lupus Erythematosis	1.11	0.85	1.41
Multiple Sclerosis	1.03	0.70	1.47
Ulcerative colitis	1.68	1.43	1.97
Crohn's Disease	1.73	1.41	2.12
Parkinson's Disease	0.52	0.45	0.60
Alzheimer's Disease	0.43	0.38	0.50
Dementia	0.41	0.36	0.46

Note: we adjusted odd ratios by age, gender, race, and length of enrollment by logistic regression model, although we matched case and control by group of age and enrollment already, to remove residual confounding we include age (Year) and length of enrollment (year) as continuous covariates in the model. One year increase in age was associated 2-3% higher risk of pancreatic cancer while one year increase in length of enrollment 4-5% lower risk.

Table 5. Coronary heart disease in combination with other related diseases in association with pancreatic cancer adjusted by age, gender, race, and length of enrollment

Characteristics	OR	95% CI	
Coronary Heart Disease	1.44	1.38	1.50
Coronary Heart Disease	1.25	1.19	1.30
Hyperlipidemia	2.23	2.16	2.29
Coronary Heart Disease	1.21	1.16	1.27
Hypertension	2.04	1.98	2.10
Coronary Heart Disease	1.44	1.38	1.50
Stroke	1.00	0.95	1.05
Coronary Heart Disease	1.35	1.29	1.41
COPD	1.45	1.40	1.51
Coronary Heart Disease	1.29	1.23	1.34
Diabetes	1.85	1.79	1.91
Coronary Heart Disease	1.29	1.24	1.34
Hyperlipidemia	2.07	2.01	2.13
Hypertension	1.12	1.07	1.17
Coronary Heart Disease	1.07	1.03	1.12
Hyperlipidemia	1.86	1.80	1.91
Hypertension	1.64	1.59	1.69
Diabetes	1.51	1.46	1.56
Coronary Heart Disease	1.09	1.05	1.14
Hyperlipidemia	1.90	1.84	1.96
Hypertension	1.71	1.66	1.76
COPD	1.27	1.22	1.31
Coronary Heart Disease	1.09	1.04	1.14
Stroke	0.81	0.77	0.86
Hyperlipidemia	1.86	1.80	1.91

Hypertension	1.66	1.61	1.71
Diabetes	1.53	1.48	1.58
Coronary Heart Disease	1.04	1.00	1.09
Hyperlipidemia	1.85	1.79	1.90
Hypertension	1.61	1.57	1.66
COPD	1.24	1.20	1.29
Diabetes	1.49	1.45	1.54

Note: in table 5, we run logistic model separately with age, gender, race , and length of enrollment as covarites for a single disease such as coronary heart disease or combination of diseases or a combination of diseases such as coronary heart disease and diabetes together.

Table 6. Sensitivity analysis of odd ratio of diabetes, liver diseases, and pancreatitis in association with pancreatic cancer adjusted by age, gender, race, and length of enrollment

Characteristics	OR	95% CI		OR	95% CI		OR	95% CI	
Time of diagnosis	Before index year			1 year before index year			3 year before index year		
Diabetes	2.08	2.02	2.15	1.89	1.83	1.95	1.66	1.60	1.72
Liver Diseases	6.29	6.01	6.57	2.07	1.94	2.20	1.80	1.66	1.95
Pancreatitis	30.03	28.43	31.73	5.37	4.98	5.78	3.20	2.87	3.56

Note: we pulled diagnosis of non-cancer chronic diseases in different exposure time period before the index year, the odds ratios of most diseases were stable, but the odd ratios of diabetes, liver diaseases, and pancreatitis declined with longer time period. Here the diagnosises was not mutual exclusive, for example, a beneficiary had diagnosis of pancreatitis before index year could had diagnosis of pnacreatitis one year before index year and/or three year before index year.

Appendix

Appendix A. Diagnostic Codes Used to Define Associated Diseases

Coronary Heart Disease (CHD)	410.xx, 413.xx
Stroke	430.xx, 431.xx, 434.xx, 436.xx, 433.x1
Hyperlipidemia	272.0x, 272.1x, 272.2x, 272.3x, 272.4x
Hypertension	401.xx, 402.xx, 403.xx, 404.xx, 405.xx
Heart failure	428.xx
COPD	490.xx, 491.xx, 492.xx, 494.xx, 495.xx, 496.xx
Diabetes	250.xx
Liver Diseases	570.xx, 571.xx, 572.xx, 573.xx, 121.1x, 751.62
Pancreatitis	577.xx
Diverticulitis	562.xx
Appendicitis	540.xx
Asthma	493.xx
Allergic rhinitis	477.xx
Atopic dermatitis	691.8x
Allergic urticaria	708.0x
Rheumatoid Arthritis	714.0x
Systematic Lupus Erythematosis	710.0x
Multiple Sclerosis	340.xx
Crohn's Disease	555.xx
Ulcerative colitis	556.xx
Parkinson's Disease	332.xx
Alzheimer's Disease	331.0x
Dementia	290.xx

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Chapter 3: Association of pancreatic cancer and prior diabetes

INTRODUCTION

There is controversy as to whether diabetes is a risk factor for pancreatic cancer or a consequence of the cancer.[1,2] Type 2 diabetes is a chronic disease which shares risk factors, especially obesity, with pancreatic cancer, and like pancreatic cancer, occurs more frequently in blacks than whites. From 1980 through 2011, the US the age-adjusted prevalence of diagnosed diabetes increased from 4.0% to 9.9% in black males, and from 4.9% to 9.0% in black females compared with white males (from 2.5% to 6.5%) and white females (from 2.6% to 5.4%). Prevalence of diabetes in Asians living in the US rose from 1997 to 2011 (4.3% to 7.8% in male, and 3.7 to 5.5% in female) making it only slightly more common than in whites.[3] Prevalence of diabetes has increased rapidly in recent decades in conjunction with the obesity epidemic while frequency of pancreatic cancer has remained stable. Increasing evidence shows long-term diabetes (> 2 years before pancreatic cancer is diagnosed) is a risk factor for pancreatic cancer, and newly diagnosed diabetes (<= 2 years before pancreatic cancer is diagnosed) may be an early manifestation of pancreatic cancer. A case-control study among Black males showed, the combination of smoking, long-term diabetes, and family history contributed 46% of pancreatic cancer, compared with 37% among White male. [4] Another study showed that old persons with new onset diabetes have about 8 fold higher risk of developing pancreatic cancer than the general population.[5] Since it is difficult to distinguish diabetes caused by pancreatic cancer from other diabetes, it is critical to identify the optimal subpopulation for screening for pancreatic cancer. A case-control study showed

in older subjects (age >65 years) without family history , but with new-onset diabetes, weight loss > 2kg or BMI<25 kg/m(2), pancreatic cancer could be distinguish at 80.8% sensitivity, 67.6% specificity, 2.5% positive predictive value and 99.7% negative predictability. [6] In view of these findings we were interested in investigating the role of new-onset diabetes and long-term or old diabetes in risk profile of pancreatic cancer.

In this study, we used the large sample available in the SEER –Medicare data and controls without pancreatic cancer enrolled in Medicare to evaluate the possible role of prior diabetes in risk profile of pancreatic cancer. We measured the strength of association between newly diagnosed diabetes and pancreatic cancer and between long-term diabetes and pancreatic cancer in the overall SEER population and in the populations of different race and ethnicity. We also estimate the proportion of cases of pancreatic cancer that could theoretically be detected by screening newly diagnosed diabetics if a 100% sensitive screening test were to become available.

METHODS

Design and Population

As in Chapter 2, a case-control study design was applied in the SEER-Medicare data to study the relationship between pancreatic cancer and new-onset as well as long-term diabetes. The study period was between 1991 and 2011 to take advantage of the expansion of SEER through the addition of four cancer registries in 2001 in four states: California, Louisiana, Kentucky, and New Jersey, which increased SEER coverage to 26% of US population.

Selection of Cases and Controls

Medicare beneficiaries who were diagnosed with pancreatic cancer in the years 1994-2011 and were 65-89 years of age at diagnosis were identified as potential cases, and the year of first diagnosis was used to define an "index" year. Only those enrolled continuously in Medicare Parts A and B for at least three consecutive calendar years before the index year were retained. As before, pancreatic cancer was defined based on *International Classification of Diseases for Oncology, the third Edition (ICD-O-3).* The primary site code included 250-254 and 257-259, and the histologic type (ICD-O-3) included 8010-8012,8015,8020-8022,8140-8141,8143,8147,8210-8211,8230-8231,8260-8263,8440,8450,8452-8453,8470-8471,8480-8481,8490,8503-8504,8507-8508,8510,8514,8521,8560,8562,8570-8576.

Potential controls were selected from a 5% non-cancer random sample of Medicare beneficiaries who resided in the same geographic areas covered by the SEER cancer registries and who were between the ages of 65 and 89. A randomly selected year from continuous enrollment of Part A and Part B was defined as the index year, and eligible controls were required to be enrolled continuously for three consecutive calendar years prior to that randomly selected index year. New-onset diabetes was defined as initial diabetes diagnosed within two years of index year with no evidence of a diabetes diagnosis in the Medicare records which had to extend back at least one year before the diagnosis of diabetes (one year of clean period). For example, to define new-

onset diabetes, for a patient with diagnosis of diabetes in 1992 and index year of 1994, 1991 was required to be free of any claims with a diagnosis of diabetes.

Cases and controls were stratified on age and length of enrollment in five year groups and controls were frequency matched to the case distribution across these strata in a 5:1 ratio. This frequency matching was done without regard to particular SEER registry..

Study Variables

Within the SEER-Medicare database the study variables used were mostly those used in Chapter 2 (please refer to the Method Section of chapter 2 for the details). Briefly:

Cases: Patients diagnosed with pancreatic cancer (from PEDSF) during 1994 to 2011 based on medical claim in the SEER-Medicare database.

Controls: Non-cancer control group from the 5% random sample of Medicare beneficiaries (from SUMDENOM files) resided in the same SEER area.

Exposure: Having diabetes diagnosis ICD 9 code of 250.xx as inpatient, outpatient, and/or physician services claims from MEDPAR, Carrier Claims File or NCH, Outpatient Claims File. At least one inpatient primary diagnosis or two separate outpatient claims (with interval >= 1 month) with the primary diagnosis code were required for identifying diabetes. The non-cancer chronic diseases other than diabetes were collected before index year with the same approach except based on their respective ICD 9 code.

Non-exposure: No diagnosis record of diabetes or other non-cancer chronic diseases between the beginning of continuous enrollment year and index year.

Statistical Analysis

We measured crude odds ratios and adjusted odds ratios by using logistic regression models to assess the strength of association of diabetes with pancreatic cancer. The adjustment covariates included age (in years), gender, race and ethnicity, as well length of continuous enrollment (in years). Although we did frequency matching on age and length of enrollment, to reduce residual confounding we further adjusted age and length of enrollment in the model. The SAS 9.3 was used for our statistical analysis.

RESULTS

A total 24,004 eligible cases with a mean age (+/- SD) of 77.6 +/- 5.4 years and a mean length of enrollment of 9.65 +/- 4.24 years were identified. Before matching there were 361,921 eligible controls with mean age 74.1+/-6.2 years and mean length of enrollment of 11.6 years +/- 5.5 years (Figure 1, Table 1a, and Table 1b). After 5:1 frequency matching there were 24,004 cases and 120,020 controls that were closely matched on age and duration of enrollment (Table 1 and 2).

As shown in Table 3, most beneficiaries of our study population were White (83.55% of cases, 82.23% of controls). The percentage of Blacks was higher in cases than in controls (9.48% vs. 7.64%). Since there were relatively few Hispanic, Asian, Native American, and other race subjects, we combined these into one category as "Others" which also comprised a lower percentage of cases than controls (6.81% vs.

9.85%). Most non-cancer chronic diseases had higher prevalence in patients with pancreatic cancer than in controls: coronary heart disease (15.32% vs.11.12%), stroke (11.27% vs. 9.40%), hyperlipidemia (45.89% vs. 31.92%), hypertension (59.09% vs. 44.97%), COPD (23.00% vs. 17.12%), new-onset diabetes within two year of index year (9.56% vs. 6.73%), old diabetes of greater than two years before index year (23.06% vs. 13.13%), diverticulitis (17.98% vs. 9.47%), liver diseases including alcoholic hepatitis and liver cirrhosis (16.65% vs. 3.48%), and pancreatitis (26.88% vs. 1.39%). However, allergy and autoimmune diseases tended to have slightly higher prevalence in cases than in controls, such as asthma (7.27% vs. 6.04%), allergic rhinitis (9.11% vs. 7.47%), rheumatoid arthritis (3.26% vs. 2.81%), and Crohn's disease (0.60% vs. 0.34%), but not multiple sclerosis which was more common in controls (0.13% vs. 0.17%); while neurodegenerative diseases were considerably less common among pancreatic cancer patients than in controls: Parkinson Disease (1.00% vs. 1.72%), Alzheimer Disease (1.18% vs. 2.61%), and dementia (1.55% vs. 3.37%). When we did a sensitivity analysis by excluding beneficiaries with pancreatitis and/or liver diseases, the distribution of demographics and other chronic diseases was similar to the distribution including pancreatitis and liver diseases. For example, coronary heart diseases prevalence was 13.15% in cases and 10.49% in controls.

The crude and adjusted odds ratios measuring the association between diabetes and pancreatic cancer showed new-onset diabetes (crude OR: 1.46, 95% CI: 1.39-1.54; adjusted OR: 1.42, 95% CI: 1.35-1.49) had a lower relative risk of pancreatic cancer compared with long-term or old diabetes (crude OR: 1.98, 95% CI: 1.92-2.05; adjusted

OR: 2.07, 95% CI: 2.00-2.15) (Table 4a). When we performed sensitivity analysis by extending the interval between diabetes and pancreatic cancer from two years to five years, the new-onset diabetes within five years of pancreatic cancer had similar crude and adjusted odds ratios (crude OR: 1.40, 95% CI: 1.34-1.47; adjusted OR: 1.37, 95% CI: 1.31-1.43), and still had a relative risk that was lower compared with long-term diabetes that occurred more than five years before pancreatic cancer (crude OR: 1.96, 95% CI: 1.87-2.05; adjusted OR: 2.05, 95% CI: 1.96-2.15).

To further study the role of diabetes in different race and ethnic populations, we estimated the odds ratios separately (Table 4b). Whites with new-onset diabetes had a higher risk of pancreatic cancer (adjusted OR: 1.52, 95% CI: 1.44-1.60) compared with Blacks, Asian, Hispanic, Native American, and other races. However, for old diabetes, the risks were similar and about two fold higher among all the races and ethnicities, although Blacks had higher risk (OR: 2.53, 95% CI: 2.28-2.82) (Table 4b). We also did sensitivity analysis by extending the interval between diabetes and pancreatic cancer from two years to five years, and we had similar findings (results not shown).

We studied the differences in characteristics of populations of non-cancer beneficiaries with new-onset diabetes, old diabetes, and no diabetes (Table 5). The three populations had similar distribution of age (new-onset diabetes: 77.01+/-5.60 years; old diabetes: 78.56+/-5.30 years; no diabetes: 77.07+/-5.73) and gender (female: 58.56%, 59.47%, 60.48%). The same distribution in race and ethnicity were found in the cohorts of new-onset diabetes and old diabetes in White (76.25% vs. 77.39%), Black (10.93% vs. 10.23%), Hispanic (3.25% vs. 3.31%), Asian (6.21% vs. 5.60%), Native

American (0.36% vs. 0.39%), and other races (2.50% vs. 2.89%). However, the beneficiaries without diabetes had higher percentage of White (83.52%), but lower percentage in Black (6.94%), Hispanic (2.08%), and Asian (4.42%). In addition, for the non-cancer chronic diseases, the prevalence was highest in the cohort of old diabetes, lowest in the cohort without diabetes, and in middle position in the cohort of new-onset diabetes. For example, the prevalence of coronary heart diseases (CHD) was 22.16% in the cohort of old diabetes, 15.05% in new-onset diabetes, but only 8.90% in the cohort without diabetes (Table 5). The similar distributions were found if we extended the interval of diagnosis of diabetes to diagnosis of pancreatic cancer from two years to five years (results not shown here); or if we excluded beneficiaries with pancreatitis and liver diseases, the prevalence of coronary heart disease was 20.84% in the cohort of old diabetes, 15.26% in new-onset diabetes, and 8.53% in the cohort without diabetes. Our data are not very encouraging with respect to the use of new diabetes as a marker for potential screening for pancreatic cancer. An approximate way of considering this is as follows: As per Table 3, 6.73% of controls from the general Medicare population had developed diabetes within the preceding two years. Assuming they are representative of the target population, and that a screening test with 100% sensitivity was available, screening these persons with recent onset diabetes would detect 9.56% of the cases (Table 3). Since the pancreatic cancer incidence rate for SEER male subjects in the 70-79 age range is about 75 per 100,000 (ref: http://ci5.iarc.fr/CI5I-X/old/table4.asp?registry=8402499&female=2&volume=1020032007&submit=Execute. Accessed January 3, 2018) a screening program in a male population of 100,000 that enrolled only the recent onset diabetics would need to screen about 6730 persons and

would detect about 10 of the 75 pancreatic cancers (20 of 150 if screening were done every two years). If test sensitivity was less than 100% some of the ten cases would be missed and, of course, there is no certainty that all ten could be successfully treated. The yield in a population of women would be slightly lower.

DISCUSSION

In our population-based case-control study, matched on age and length of enrollment in traditional fee-for-service Medicare, we found 9.56% pancreatic cancer patients had new-onset diabetes within 2 years of the diagnosis of pancreatic cancer, and 23.06% had old diabetes greater than 2 years before the diagnosis of pancreatic cancer compared with 6.73% and 13.13% respectively in control. Therefore, our study showed a total of about 33% patients of pancreatic cancer had diabetes at the time of diagnosis, which is somewhat lower than the 47% and 68% prevalence of diabetes among pancreatic cancer patients reported by Aggarwal et al. Their higher percentage of diabetes might be related to their much smaller sample sizes (N=111 and N=500). [7,8] Our study showed patients with diabetes had increased risk of pancreatic cancer measured by either crude odds ratio (OR) or adjusted OR, and they were similar with two year or five year intervals. A pooled analysis of three large case-control studies showed that with increased duration of diabetes, the risk of pancreatic cancer decreased (≤2 years OR: 2.9, 95% CI: 2.1–3.9; 3–5 years OR: 1.9, 95% CI: 1.3–2.6; 6–10 years OR: 1.6, 95% CI: 1.2-2.3; 11-15 years OR: 1.3, 95% CI: 0.9-2.0; > 15 years OR: 1.4, 95% CI: 1.0-2.0). [9] Gupta et al. reported relative risk (RR) of pancreatic cancer among patients of new-onset diabetes was highest in the first 2 years in a large cohort

study compared with nondiabetics, although the change of the adjusted RR by age, sex, and race/ethnicity was not linear from year 1 to year 6 with OR of 3.91 (95% CI: 2.93-5.23), 2.75 (95% CI: 1.94-3.88), 1.17 (95% CI: 0.69-1.99), 1.60 (95% CI: 1.01-2.54), 2.25 (95% CI: 1.51-3.35), and 0.68 (95% CI: 0.25-1.81). [10] However, Brodovicz et al. found that incidence of pancreatic cancer was significantly higher in patients with diabetes longer than 5 years (123.69 per 100,000 person years) compared with shorter duration (71.32 to 78.76 per 100,000 person years).[11] The findings of the case-control study by Silverman et al also showed an increasing trend of increasing interval between onset of diabetes and diagnosis of pancreatic cancer for at least 10 years (0-1 years: 1.3, 2-4 years: 1.4, 5-9 years: 1.7, and >= 10 years: 1.5) after adjustment of age, gender, area, cigarette smoking, alcohol consumption, body mass index and calories from food. [12]

Our findings support the importance of long-standing diabetes in pancreatic cancer, which suggests that diabetes may contribute to the causation of the cancer or may be associated with undefined pancreatic abnormalities that are themselves also associated with cancer. In this very large, population based study there was no evidence that recent onset diabetes was more strongly associated with cancer incidence than diabetes of long duration. However, we could not address this issue more definitively with survival analysis since, for the majority of cases, we had no data on the onset of diabetes. It remains to be seen, when practical screening tests are developed, whether screening patients with long-standing diabetes would detect cancers that are too advanced to treat, or whether screening patients with new diabetes might miss early cancers that are too small to detect.

After stratification by race or ethnicity, the association between new-onset diabetes and pancreatic cancer was strongest in Whites. Age adjusted incidence of diabetes increased in Whites from 1997 to 2008 in conjunction with the obesity epidemic and has subsequently decreased, [13] trends that overlapped substantially with our study period (1991-2011). Although it is not known whether this changing incidence is associated with changing relative risk for pancreatic cancer, the higher odds ratio for recent onset diabetes in whites is of interest.

CONCLUSION

In this very large population-based case-control study of older Americans, we found highly significant, adjusted odds ratios of 2.07 and 1.46 for diabetes of >2 years and <=2 years duration, respectively. The robust association between diabetes and pancreatic cancer is not understood and remains an important target for further investigation However, it does not appear likely that diabetes by itself will be a very satisfactory way to target any future screening program.

TABLES and FIGURES

Figure 1. Flowchart of case and control selection

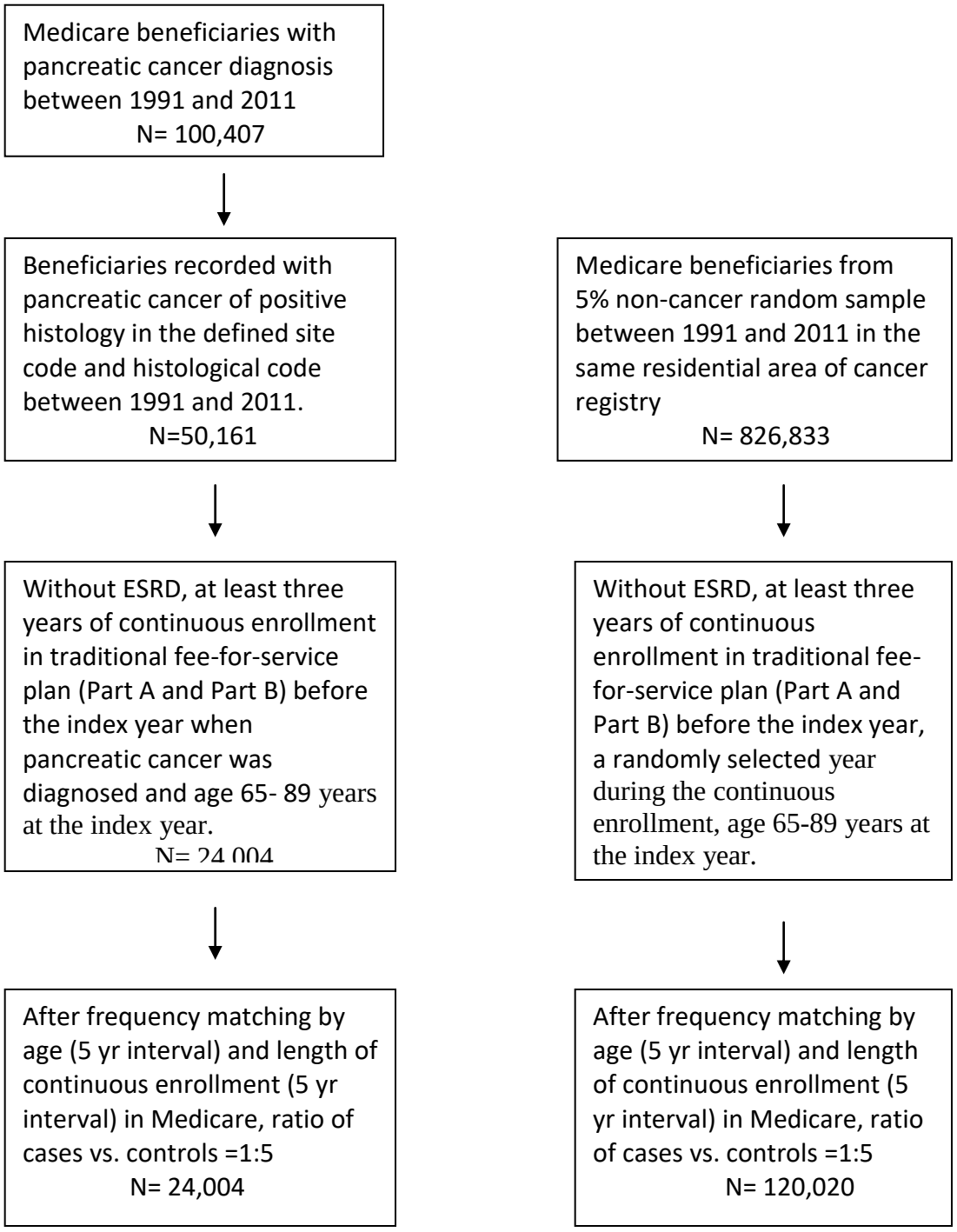

Table 1a. Age distribution among case and control

	Before matching			
	Case		Control	
Age (Year)	N	%	N	%
65-69	1,325	5.52	104,955	29.00
70-74	6,574	27.39	105,718	29.21
75-79	7,374	30.72	72,534	20.04
80-84	5,670	23.62	50,366	13.92
85-89	3,061	12.75	28,348	7.83
Total	24,004	100.00	361,921	100.00
	After matching			
	Case		Control	
65-69	1,325	5.52	6,625	5.52
70-74	6,574	27.39	32,870	27.39
75-79	7,374	30.72	36,870	30.72
80-84	5,670	23.62	28,350	23.62
85-89	3,061	12.75	15,305	12.75
Total	24,004	100.00	120,020	100.00

Note: for matching, cases and controls were grouped by both age (5 years interval) and length of enrollment (5 years interval), we included all cases of 24,004 for matching, and randomly selected controls from each age and enrollment group from control to match cases in the corresponding age and enrollment group from case at 5:1 ratio.

Table 1b. Average age in case and control

	N	Mean	STD	Median	Quartile Range	Minimum	Maximum
			Before matching				
Case	24,004	77.58	5.41	77.00	9.00	65.00	89.00
Control	361,921	74.14	6.16	73.00	10.00	65.00	89.00
			After matching				
Case	24,004	77.58	5.41	77.00	9.00	65.00	89.00
Control	120,020	77.26	5.69	77.00	10.00	65.00	89.00

See footnotes to Table 1a

Table 2a. Length of enrollment among case and control

	Before matching			
	Case		Control	
Length of Enrollment (Year)	N	%	N	%
1-4	4,924	20.51	57,758	15.96
5-9	7,837	32.65	94,538	26.12
10-14	7,524	31.34	102,925	28.44
15-19	3,370	14.04	65,508	18.10
>= 20	349	1.45	41,192	11.38
Total	24,004	100.00	361,921	100.00
	After matching			
	Case		Control	
1-4	4,924	20.51	24,620	20.51
5-9	7,837	32.65	39,185	32.65
10-14	7,524	31.34	37,620	31.34
15-19	3,370	14.04	16,850	14.04
>= 20	349	1.45	1,745	1.45
Total	24,004	100.00	120,020	100.00

See footnotes to Table 1a

Table 2b. Average length of enrollment in case and control

	N	Mean	STD	Median	Quartile Range	Minimum	Maximum
			Before matching				
Case	24,004	9.65	4.24	9.00	7.00	4.00	22.00
Control	361,921	11.55	5.54	11.00	9.00	4.00	23.00
			After matching				
Case	24,004	9.65	4.24	9.00	7.00	4.00	22.00
Control	120,020	9.87	4.42	9.00	7.00	4.00	23.00

See footnotes to Table 1a

Table 3. Demographic and non-cancer chronic disease characteristics

	Case (N=24,004)		Control (N=120,020)	
	Mean/N	STD/%	Mean/N	STD/%
Age	77.58	5.41	77.26	5.69
Gender				
Female	12,575	52.39	72,278	60.22
Race				
White	20,056	83.55	98,689	82.23
Black	2,276	9.48	9,167	7.64
Others (sum of below races or ethnicity)	1,635	6.81	11,826	9.85
Hispanic	402	1.67	2,789	2.32
Asian	740	3.08	5,631	4.69
Native American	53	0.22	356	0.30
Other races	440	1.83	3,050	2.54
Non-cancer chronic diseases				
Coronary Heart Disease (CHD)	3,678	15.32	13,346	11.12
Stroke	2,705	11.27	11,280	9.40
Hyperlipidemia	11,015	45.89	38,313	31.92
Hypertension	14,183	59.09	53,972	44.97
COPD	5,520	23.00	20,542	17.12
New-onset diabetes (<=2 yrs)	2,294	9.56	8,080	6.73
Old diabetes (> 2 yrs)	5,536	23.06	15,755	13.13
Liver Diseases	3,996	16.65	4,175	3.48
Pancreatitis	6,452	26.88	1,663	1.39
Diverticulitis	4,316	17.98	11,370	9.47
Appendicitis	139	0.58	448	0.37
Asthma	1,744	7.27	7,249	6.04
Allergic rhinitis	2,187	9.11	8,960	7.47
Atopic dermatitis	445	1.85	1,734	1.44
Allergic urticaria	108	0.45	433	0.36
Rheumatoid Arthritis	782	3.26	3,367	2.81
Systematic Lupus Erythematosis	79	0.33	393	0.33
Multiple Sclerosis	31	0.13	210	0.17
Crohn's Disease	144	0.60	408	0.34
Parkinson's Disease	240	1.00	2,068	1.72
Alzheimer's Disease	283	1.18	3,136	2.61
Dementia	372	1.55	4,048	3.37

Note: based on 24,004 cases and 120,020 controls after matching of age and length of enrollment; The race "Others" included Hispanic, Asian, Native American, and other races as a combined race group to increase sample size for later analysis of odd ratios; non-cancer chronic diseases were defined by two outpatient primary diagnosis ICD 9 code (Appendix A) at least 30 days apart or one inpatient primary diagnosis one year before index year.

Table 4a. Association between diabetes and pancreatic cancer

Diabetes	**Crude OR**	**95% CI**	
New-onset diabetes (<=2 yrs)	1.46	1.39	1.54
Old diabetes (> 2 yrs)	1.98	1.92	2.05
Diabetes	**Adjusted OR**	**95% CI**	
New-onset diabetes (<=2 yrs)	1.42	1.35	1.49
Old diabetes (> 2 yrs)	2.07	2.00	2.15

Note: adjusted odds ratios were from logistic regression model with adjustment of age, gender, race, and length of enrollment

Table 4b. The association between diabetes and pancreatic cancer stratified by race or ethnicity

Race or ethnicity	**New-onset diabetes**			**Old diabetes**		
	OR	**95% CI**		**OR**	**95% CI**	
White (n=118,745)	1.52	1.44	1.60	2.01	1.94	2.09
Black (n=11,443)	1.01	0.87	1.18	2.53	2.28	2.82
Asian (n=6,371)	1.17	0.90	1.51	1.95	1.62	2.34
Hispanic (n=3,191)	1.27	0.90	1.76	1.92	1.51	2.44
Native American (n=409)	0.18	0.01	0.91	2.34	1.84	2.98
Other races (n=3,490)	1.37	0.95	1.94	2.72	1.36	5.32

Note: odds ratios were adjusted by age, gender, and length of enrollment using logistic regression model.

Table 5. Comparisons of demographic and non-cancer chronic disease characteristics among controls of new-onset diabetes, old diabetes, and without diabetes

	New-onset Diabetes (N=8080)		Old diabetes (N=15,755)		No diabetes (N=96,185)	
	Mean/N	STD/%	Mean/N	STD/%	Mean/N	STD/%
Age	77.01	5.60	78.56	5.30	77.07	5.73
Gender						
Female	4,732	58.56	9,370	59.47	58,176	60.48
Race						
White	6,161	76.25	12,193	77.39	80,335	83.52
Black	883	10.93	1,611	10.23	6,673	6.94
Others (sum of below races or ethnicity)	996	12.33	1,921	12.19	8,909	9.26
Hispanic	263	3.25	522	3.31	2,004	2.08
Asian	502	6.21	882	5.60	4,247	4.42
Native American	29	0.36	61	0.39	266	0.28
Other races	202	2.50	456	2.89	2,392	2.49
Non-cancer chronic diseases						
Coronary Heart Disease (CHD)	1,289	15.95	3,492	22.16	8,565	8.90
Stroke	1,118	13.84	2,923	18.55	7,239	7.53
Hyperlipidemia	2,590	32.05	8,472	53.77	27,251	28.33
Hypertension	4,776	59.11	11,299	71.72	37,897	39.40
COPD	1,683	20.83	4,241	26.92	14,618	15.20
Liver Diseases	371	4.59	1,273	8.08	2,531	2.63
Pancreatitis	130	1.61	492	3.12	1,041	1.08
Diverticulitis	769	9.52	2,456	15.59	8,145	8.47
Appendicitis	27	0.33	80	0.51	341	0.35
Asthma	548	6.78	1,630	10.35	5,071	5.27
Allergic rhinitis	536	6.63	1,797	11.41	6,627	6.89
Atopic dermatitis	100	1.24	373	2.37	1,261	1.31
Allergic urticaria	29	0.36	86	0.55	318	0.33
Rheumatoid Arthritis	269	3.33	766	4.86	2,332	2.42
Systematic Lupus Erythematosis	33	0.41	81	0.51	279	0.29
Multiple Sclerosis	14	0.17	42	0.27	154	0.16
Crohn's Disease	19	0.24	92	0.58	297	0.31

Parkinson's Disease	152	1.88	389	2.47	1,527	1.59
Alzheimer's Disease	214	2.65	560	3.55	2,362	2.46
Dementia	366	4.53	769	4.88	2,913	3.03

Note: based on 24,004 cases and 120,020 controls after matching of age and length of enrollment; The race “Others” included Hispanic, Asian, Native American, and other races as a combined race group to increase sample size for later analysis of odd ratios; non-cancer chronic diseases were defined by two outpatient primary diagnosis ICD 9 code (Appendix A) at least 30 days apart or one inpatient primary diagnosis one year before index year.

Appendix

Appendix A: ICD 9 code for non-cancer chronic diseases

Coronary Heart Disease (CHD)	410.xx, 413.xx
Stroke	430.xx, 431.xx, 434.xx, 436.xx, 433.x1
Hyperlipidemia	272.0x, 272.1x, 272.2x, 272.3x, 272.4x
Hypertension	401.xx, 402.xx, 403.xx, 404.xx, 405.xx
Heart failure	428.xx
COPD	490.xx, 491.xx, 492.xx, 494.xx, 495.xx, 496.xx
Diabetes	250.xx
Liver Diseases	570.xx, 571.xx, 572.xx, 573.xx, 121.1x, 751.62
Pancreatitis	577.xx
Diverticulitis	562.xx
Appendicitis	540.xx
Asthma	493.xx
Allergic rhinitis	477.xx
Atopic dermatitis	691.8x
Allergic urticaria	708.0x
Rheumatoid Arthritis	714.0x
Systematic Lupus Erythematosis	710.0x
Multiple Sclerosis	340.xx
Crohn's Disease	555.xx
Ulcerative colitis	556.xx
Parkinson's Disease	332.xx
Alzheimer's Disease	331.0x
Dementia	290.xx

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