Diabetes-related complications and pancreatic cancer incidence in the Multiethnic Cohort

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ABSTRACT

Background: People with diabetes are at an increased risk of developing pancreatic cancer. However, it is unclear whether diabetes-related complications are associated with risk of pancreatic cancer.

Methods: A nested matched case-control analysis was conducted among the fee-for-service Medicare participants of the prospective Multiethnic Cohort (N~123,000). Between 2001-2014, 433 incident cases of pancreatic ductal adenocarcinoma (PDAC) were matched to 1,728 controls by birth year, sex, race/ethnicity, and age at cohort entry. Participants were linked to data from the California and Hawaii cancer registries and Medicare claims. We used the diabetes complications severity index (DCSI) for the presence of 7 complications within two-years prior to the diagnosis date of the index case. Multivariable conditional logistic regression was used to examine the association of DCSI with pancreatic cancer incidence.

Results: Diabetes was present among 45.4% of cases and 34.1% of controls. Cases had higher DCSI score compared to controls (score ≥4: 32.8% in cases; 21.2% in controls). The most prevalent diabetes-related complications for cases were cardiovascular disease (61.2%), nephropathy (31.2%), and cerebrovascular disease (21.7%). Individuals with diabetes (OR: 1.48, 95% CI:1.14-1.91), nephropathy (OR:1.75, 95% CI:1.32-2.33), cardiovascular disease (OR:1.88, 95% CI:1.45-2.44), and metabolic complications (OR:6.61, 95% CI:2.49-17.50) were at increased risk of pancreatic cancer. For every 1-unit increase in DCSI score, participants had 18% greater risk of pancreatic cancer (OR: 1.18, 95% CI:1.11-1.25).
**Conclusions:** Participants with diabetes-related complications have an elevated risk of pancreatic cancer. Identifying diabetes-related complications may help identify high-risk groups who can be studied for development of early markers for this fatal cancer.
Pancreatic cancer is one of the most fatal cancers with an estimated 56,000 new cases and 45,000 deaths associated with the disease in 2019.\(^1\) According to the National Cancer Institute’s Surveillance, Epidemiology, and End Results registry, the five-year survival rate for pancreatic cancer is 9.3% in 2019. By 2030, pancreatic cancer is predicted to be the second most fatal cancer after lung cancer.\(^2\) Since there are no screening tests to detect pancreatic cancer and patients only experience symptoms with advanced-stage disease, there is a critical need to identify epidemiological risk factors and groups at the highest risk of developing the disease.

Known risk factors for pancreatic cancer include smoking\(^3\)–\(^5\), family history of pancreatic cancer,\(^3,5\) and obesity.\(^3,5\)–\(^7\)

Diabetes is known to increase the risk of pancreatic cancer,\(^5,8\)–\(^11\) especially among patients diagnosed after the age of 50.\(^12\) However, most of these studies only measure the presence or absence of diabetes without taking into consideration the severity or heterogeneity of the condition. Uncontrolled and unmanaged diabetes often results in complications such as retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular, and metabolic disease.\(^13\)–\(^16\) Diabetes complications have been linked to higher health care costs, utilization and mortality compared to diabetes with no complications\(^14,16\) but to our knowledge, have not been studied in relation to pancreatic cancer.

African Americans,\(^17\) Latinos,\(^17\) and Japanese Americans\(^18\) are at a high risk of developing diabetes and are more likely to have a higher prevalence of severe diabetes complications compared to non-Hispanic whites.\(^15\) The reason for severe diabetes among minorities may be due to an underutilization of primary care physicians, poor medication adherence, and poor
understanding of their disease.\textsuperscript{19-21} While African Americans have the highest incidence of pancreatic cancer in the US\textsuperscript{22} and have the highest prevalence of diabetes, the comparably high rate in Latinos is inconsistent with their low rate of pancreatic cancer. This suggests that measuring the presence or absence may not entirely explain the true risk of pancreatic cancer due to glucose abnormalities and identifying complications from diabetes may help identify high-risk groups.

Understanding the role of diabetes in the etiology of pancreatic cancer can be helpful in targeting efforts to identify populations at high-risk such as racial/ethnic minorities who have a higher prevalence of diabetes compared to non-Hispanic whites in the population. However, the relationship between diabetes-related complications and pancreatic cancer is unknown. Therefore, the goal of this study was to investigate whether elevated risk of pancreatic cancer is observed in patients with diabetes-related complications.

**METHODS**

**Study population**

The Multiethnic Cohort (MEC) is an ongoing population-based prospective cohort study of over 215,000 participants from Hawaii and California, assembled between 1993-1996. The MEC was established to study cancer etiology by collecting detailed information on diet and other lifestyle factors and biospecimens to study genetic factors. The study design and baseline characteristics have been published elsewhere.\textsuperscript{23} Briefly, the cohort is comprised of predominately 5 racial/ethnic groups: African Americans, Native Hawaiians, Japanese Americans, Latinos, and
whites (aged 45-75 years at cohort entry). All participants completed a self-administered baseline questionnaire on demographic and lifestyle factors, physical activity, and tobacco smoking history.

The MEC was linked with the Centers for Medicaid and Medicare Services (CMS) claims data to obtain all inpatient and outpatient records for cohort members that were enrolled in Medicare Fee-for-Service (FFS) (n~123,000). The claims data contains dates of services, International Classification of Disease (ICD-9-CM) diagnosis codes and Concurrent Procedural Terminology (CPT, Version 4) codes for all billed claims. Medicare claims data between 1999 and 2016 are available in the MEC. Study protocols were approved by the Committee on Human Studies at the University of Hawaii and by the Institutional Review Board of the Keck School of Medicine of USC.

Eligible participants for the present analysis were FFS cohort members who were free of cancer at cohort entry and had complete risk factor data including smoking status, body mass index (BMI), alcohol intake, and physical activity.

**Case ascertainment and matched control selection**

We utilized a nested case-control design for this study. Cases were all incident pancreatic cancer cases (diagnosed at age 67 or older) identified among the at-risk multiethnic cohort participants with 24-months of Medicare FFS enrollment prior to their cancer diagnosis. First incident primary invasive pancreatic cancer cases (International Classification of Disease for Oncology version 3 topographic [C250-C259]) were identified from the annual linkage of cohort
participants to the California and Hawaii Tumor Registries. These cancer registries are part of the SEER program. To assure at least 24 months between exposure and cancer diagnosis, cases were required to be diagnosed at 67 years or older. Cases were diagnosed with primary pancreatic cancer occurring between 2001-2014 and enrolled in Medicare FFS for at least two consecutive years prior to their diagnosis. We restricted the analysis to pancreatic ductal adenocarcinoma (PDAC), an exocrine tumor which accounts for over 90% of all pancreatic cancers using histological type of adenocarcinoma and infiltrating pancreatic adenocarcinoma (ICD-O-3 histology codes excluding 9050-9055, 9140, or 9590-9992). A total of 433 incident cases of PDAC were included in this analysis.

Control subjects were members from the same cohort, age 65 and older, without a previous history of any cancer with 24-months of follow-up during the same time-period as the matched case. Four controls were individually matched to each case on race/ethnicity, age at cohort entry ±1-year, sex, and birth year ±1-year. All controls were cancer-free at the time of selection into the study and were enrolled in Medicare FFS for 24-months prior the date of diagnosis of the matched-case. Between 2001-2014, 433 incident cases of pancreatic ductal adenocarcinoma (PDAC) were matched to 1,728 controls by birth year, sex, race/ethnicity, and age at cohort entry.

**Diabetes Complications Severity Index**

We used the diabetes complications severity index (DCSI) developed by Young and Colleagues to assess the level of risk of adverse outcomes including hospitalizations and mortality by using diagnosed complications. A DCSI score ranges from 0-13 based on the presence and severity
of 7 categories of complications including cardiovascular disease, nephropathy, retinopathy, peripheral vascular disease, stroke, neuropathy, and metabolic complications. Metabolic complications included a diagnosis of ketoacidosis, hyperosmolar, and other coma. Each complication category is scored on a scale from 0-2, determined by the presence and severity of the complications (0=not present, 1=some abnormality, and 2=severe abnormality), except for neuropathy (scored 0-1). Diabetes and the presence or absence of each diabetes-related complication (yes or no) were identified based on ICD-9-CM codes from inpatient and outpatient Medicare claims data during the two-year period prior to a pancreatic cancer diagnosis for cases and during the same calendar period for each matched control. We identified DCSI among the entire cohort.

**Covariates**

Data on demographic and lifestyle factors including age at cohort entry (years), sex (male or female), education level (less than or equivalent to a high school diploma, some college, or college or higher), neighborhood-level SES at the census tract level for the address on file at baseline (quintiles lowest to highest), BMI (kg/m²), smoking status (never, former, current), any vigorous physical activity (yes or no), and alcohol intake (g/day) were obtained from the baseline questionnaire. We assessed non-diabetes-related comorbid conditions using Medicare claims data for the two-year period for congestive heart failure (yes or no), chronic obstructive pulmonary disease (yes or no), dementia (yes or no), paralysis (yes or no), mild liver disease (yes or no), moderate/severe liver disease (yes or no), peptic ulcer disease (yes or no), and rheumatologic disease (yes or no).
Statistical Analysis

Frequencies and means were used to compare characteristics between pancreatic cancer cases and controls. Two-sided chi-square tests were used to calculate p-values to measure the association between each covariate and race/ethnicity or DCSI score. Conditional multivariate logistic regression was used to estimate the association of pancreatic cancer with a diagnosis of diabetes and each of the complications. The association between diabetes complications, DCSI, and pancreatic cancer incidence was examined using multivariable conditional logistic regression analyses stratified by matched set and adjusted for baseline educational attainment, neighborhood-level SES, alcohol intake, smoking status, any vigorous physical activity at baseline, BMI, and other non-diabetes related comorbid conditions listed above. All analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary NC). Statistical significance was set at p<0.05.

RESULTS

In this nested multiethnic case-control study, the largest racial/ethnic group was Japanese Americans (43.5%) and majority were female (52.6%) (Table 1). The majority of study participants had attended some college or higher (54.0% among cases and 53.9% among controls), were younger than 70 years at cohort entry (76.7% among cases and 78.1% of controls), consumed less than 24 g/day of alcohol (88.5% among cases and 89.5% among controls) and were former or current smokers (54.3% among cases and 52.3% among controls).

Of the 433 PDAC cases, 21.9% had no diabetes-related complications, 13.6% had 1, 19.2% had 2, 12.4% had 3, 12.0% had 4 and 20.8% had 5 or more complications (Table 2). Among cases,
age, sex, race/ethnicity, smoking status, BMI, chronic obstructive pulmonary disease (COPD), dementia and rheumatologic disease were statistically significantly associated with DCSI (p<0.05). Among controls, age, sex, race/ethnicity, educational attainment, BMI, COPD, dementia, and rheumatologic disease were statistically significantly associated with the DCSI score (p<0.05).

In this study, diabetes was present among 45.4% of cases and 34.1% of controls. Compared to controls, cases had a DCSI of 4 or more (32.8% vs. 21.2%) and a greater proportion were diagnosed with each of the 7 complications and a greater proportion of controls had no complications (Table 3). The most prevalent diabetes-related complications for cases were cardiovascular disease (61.2%), nephropathy (31.2%), and cerebrovascular disease (21.7%). A greater proportion of PDAC cases compared to controls were diagnosed with neuropathy (19.2% vs. 13.4%) and peripheral vascular disease (18.5% vs. 12.0%). A greater proportion of Latino cases were diagnosed with diabetes (58.3%) followed by African-Americans (50.0%) compared to other racial/ethnic groups. Among African-American, Native Hawaiian, and Latino cases, about one-third (35.5%, 35.0% and 31.7% respectively), had a DCSI score of five or more, a greater proportion than any of the other racial/ethnic groups of cases. Among controls African-Americans and Latinos displayed the greatest proportion of a DCSI score of 5 or more (23.0% and 19.6%, respectively) compared to the other racial/ethnic groups. In contrast, among cases, whites had the highest proportion with a DCSI score of 0 (28.9%) followed by Japanese Americans (26.6%). The most common complication among the cases and controls was cardiovascular disease, ranging from 74.2% in African-American cases to 38.0% in Japanese
American controls. Nephropathy and cerebrovascular disease were also highly prevalent among cases.

Diabetes and complications were positively associated with pancreatic cancer (Table 4). We observed that individuals with diabetes had 48% increased odds (OR: 1.48, 95% CI 1.14-1.91) of pancreatic cancer compared to those without diabetes. Cardiovascular disease (OR: 1.88, 95% CI 1.45-2.44), nephropathy (OR: 1.75, 95% CI 1.32-2.33), and metabolic disease (6.61, 95% CI 2.49-17.50) were positively associated with pancreatic cancer risk after adjusting for demographic, lifestyle characteristics, and chronic conditions, including diabetes.

Risk of pancreatic cancer increased with increasing DCSI score (Table 5). Compared with no complications, a greater risk of pancreatic cancer was found in relation to the DCSI as follows: 1 complication OR:1.61 (95% CI 1.11-2.33), 2 complications OR:1.94 (95% CI 1.38-2.74), 3 complications OR:2.26 (95% CI 1.52-3.37), and 4 or more complications OR:2.59 (95% CI: 1.82-3.69). When we replaced DCSI categories with the count of complications as a linear variable, for every 1-unit increase in DCSI score, participants had 18% greater risk of pancreatic cancer (OR: 1.18, 95% CI:1.11-1.25). We observed that the continuous measure of DCSI (for every 1-unit increase in score) was associated with a 22-23% increased risk of pancreatic cancer among patients with (OR 1.22, 1.09-1.36) and without diabetes (OR 1.23, 1.11-1.36).

**DISCUSSION**

In our study, the number of complications from diabetes was associated with an elevated risk of pancreatic cancer even after controlling for a number of well-studied risk factors including
obesity, smoking history, and other chronic conditions. Metabolic disease, cardiovascular
disease, and nephropathy were also associated with increased risk of pancreatic cancer,
independent of other risk factors and irrespective of diabetes status.

Several epidemiological studies have reported that diabetes is associated with an increased risk
of pancreatic cancer.\textsuperscript{9,12} We know that diabetes diagnosed at a later age,\textsuperscript{12} those with incident
diabetes,\textsuperscript{12} and those with diabetes for a longer duration\textsuperscript{25} are at an increased risk of pancreatic
cancer, but these studies measured only the presence or absence of disease. To the best of our
knowledge, no studies have linked DCSI and pancreatic cancer risk. Previous epidemiological
studies have reported that DCSI and complications are associated with an increased risk of
mortality,\textsuperscript{14} more hospitalizations,\textsuperscript{14} and higher healthcare utilization\textsuperscript{15} and, that Hispanics and
African Americans have a higher prevalence of complications\textsuperscript{15} but these studies do not link
complications to risk of cancer. Our hypothesis was that complications are associated with
increased risk of pancreatic cancer as they would indicate a higher DCSI and a higher probability
of damage to the pancreas.

It remains unclear whether the association between diabetes and pancreatic cancer is due to
hyperglycemia, whether diabetes is a marker of underlying biologic factors that alter cancer risk
such as insulin resistance and hyperinsulinemia, or whether the association between cancer and
diabetes is indirect and due to common risk factors such as obesity.\textsuperscript{26} Our study suggests that
some complications such as nephropathy, cardiovascular disease, and metabolic conditions are
independently associated with pancreatic cancer incidence. Among known pancreatic cancer risk
factors, several medical conditions such as diabetes and those found in our study are associated
with increased risk pointing to a chronic inflammatory hypothesis. The hypothesis suggests that chronic conditions and complications resulting from unmanaged disease can result in chronic inflammation and the risk of pancreatic cancer should increase for those conditions that are related to inflammation. Gomez-Rubio and colleagues used a systems approach to characterize high-risk patients based on multimorbidities and found that patients who had been diagnosed with three or more metabolic conditions, including diabetes, had 61% increased odds of pancreatic cancer (95% CI: 1.11-2.35) compared to no conditions. While some complications were independently associated with pancreatic cancer, we also found a positive association between the frequency of complications and a patient’s pancreatic cancer risk.

The goal of this study was to examine the relationship between DCSI and pancreatic cancer risk and whether DCSI can be used to identify patients at high-risk and has the utility of being implemented in clinical practice without surveying patient’s self-reported chronic conditions. We cannot rule out reverse causation in our study, instead however, our study adds to the evidence that diabetes and associated complications are associated with risk of pancreatic cancer. In a sensitivity analysis, the distribution of DCSI was similar across stage at diagnosis of pancreatic cancer (not shown); therefore, the observed positive association is likely not the result of detection bias and suggests that the DCSI score is not an indicator for underlying pancreatic cancer that is not yet diagnosed. Further, we examined the DCSI in a two-year time-period and observed multiple complications, however, more longitudinal research is needed to determine if the associations are consistent with diabetes-related complications that occur well before cancer onset.
We found that African-American and Latino participants were more likely to be diagnosed with five or more diabetes complications compared to other racial/ethnic groups, which is similar to other findings. However, we also add to the literature that understudied Native Hawaiians have a higher prevalence of complications compared to whites. Our results are particularly striking since minority patients are at an increased risk of diabetes and are more likely to have uncontrolled disease with a higher prevalence of complications. This suggests that they may be at higher risk of developing pancreatic cancer. The incidence of pancreatic cancer is indeed higher for African Americans and Native Hawaiians. While we did find that Latinos were more likely to have five or more complications, evidence suggests that they do not have a higher incidence of pancreatic cancer compared to other racial ethnic groups. More research is needed to understand whether accounting for complications explains the higher incidence of pancreatic cancer in racial/ethnic minority groups.

Our study has several strengths. Our study had a large proportion of racial and ethnic minorities and we were able to account for important confounders such as obesity and smoking by using linked lifestyle baseline questionnaire data to cancer registry data and Medicare claims. Furthermore, our study used medical claims data to identify diabetes complications, which can be used to identify high-risk patients and can be translated into clinical practice.

However, our study is not without limitations. First, in this study we did not assess the pharmacological treatment of diabetes with metformin or insulin. Although the biological basis for these treatments is not fully understood, a meta-analysis of 37 studies has shown that metformin is associated with 46% reduced risk of pancreatic cancer. Metformin may reduce
the risk of cancer because it can prevent worsening diabetes and related complications. In addition, long-acting insulin compared to no insulin may be associated with an increased risk of pancreatic cancer although it may just be an indicator of long-lasting and/or severe diabetes.\textsuperscript{36}

The focus of our study, however, was to examine whether patients with complications are at an increased risk of cancer compared to those without diabetes or those with diabetes alone. Pharmacologically unmanaged disease likely results in greater complications from diabetes. Patients with a higher DCSI score may be less likely to take appropriately dosed medications than those without complications\textsuperscript{37} and would therefore, bias the observed results towards the null. Second, we did not account for the length or duration of diabetes because the goal of this study was to examine complications within 24-months of diagnosis. Given the start of Medicare coverage at age 65 only, we could not systematically ascertain the time of first diabetes for all cohort members. Finally, our study included a racially diverse group of people from a large prospective cohort study who were enrolled in Medicare FFS and over 65. As Medicare-eligible individuals covered by HMO plans, e.g., Kaiser, may have different risk factor and disease profiles, findings in this populations may have been different and although approximately two-thirds of pancreatic cancer cases are over the age of 65 and the average age at the time of diagnosis is 70 years,\textsuperscript{1} our study results should not be generalized to people outside of this group.

In conclusion, our results in the MEC suggest that diabetes-related complications are associated with an elevated risk of pancreatic cancer compared to patients without complications. The results suggest the utility of the DCSI to assess risk of pancreatic cancer when medical claims are readily available, particularly for health plan administrators, provider practices, and researchers. Furthermore, more long-term longitudinal research is needed in order to rule out whether
diabetes-related complications are capturing underlying pancreatic cancer and to examine whether the DCSI score can be used as a way to identify and potentially screen high-risk patients.

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REFERENCES

1. American Cancer Society. *Facts & Figures 2019*. Atlanta, GA: American Cancer Society; 2019.

2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res.* 2014;74(11):2913-2921.

3. Arnold LD, Patel AV, Yan Y, et al. Are racial disparities in pancreatic cancer explained by smoking and overweight/obesity? *Cancer Epidemiol Biomarkers Prev.* 2009;18(9):2397-2405.

4. MacMahon B. Risk factors for cancer of the pancreas. *Cancer*. 1982;50(11 Suppl):2676-2680.

5. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. *Int J Epidemiol.* 2015;44(1):186-198.

6. Nöthlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Body mass index and physical activity as risk factors for pancreatic cancer: the Multiethnic Cohort Study. *Cancer Causes Control.* 2007;18(2):165-175.

7. Nöthlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Vegetable intake and pancreatic cancer risk: the multiethnic cohort study. *Am J Epidemiol.* 2007;165(2):138-147.

8. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *British Journal of Cancer.* 2005;92:2076-2083.

9. Ben Q, Xu M, Ning X, et al. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. *Eur J Cancer.* 2011;47(13):1928-1937.

10. Cui Y, Andersen DK. Diabetes and pancreatic cancer. *Endocr Relat Cancer.* 2012;19(5):F9-F26.

11. Eibl G, Cruz-Monserrate Z, Korc M, et al. Diabetes Mellitus and Obesity as Risk Factors for Pancreatic Cancer. *J Acad Nutr Diet.* 2018;118(4):555-567.

12. Setiawan VW, Stram DO, Porcel J, et al. Pancreatic Cancer Following Incident Diabetes in African Americans and Latinos: The Multiethnic Cohort. *J Natl Cancer Inst.* 2019;111(1):27-33.

13. Selby JV, Karter AJ, Ackerson LM, Ferrara A, Liu J. Developing a prediction rule from automated clinical databases to identify high-risk patients in a large population with diabetes. *Diabetes Care.* 2001;24(9):1547-1555.

14. Young BA, Lin E, Von Korff M, et al. Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization. *Am J Manag Care.* 2008;14(1):15-23.

15. Hazel-Fernandez L, Li Y, Nero D, et al. Racial/ethnic and gender differences in severity of diabetes-related complications, health care resource use, and costs in a Medicare population. *Popul Health Manag.* 2015;18(2):115-122.

16. Hazel-Fernandez L, Li Y, Nero D, et al. Relationship of diabetes complications severity to healthcare utilization and costs among Medicare Advantage beneficiaries. *Am J Manag Care.* 2015;21(1):e62-70.

17. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and Trends in Diabetes Among Adults in the United States, 1988-2012. *JAMA.* 2015;314(10):1021-1029.
18. Maskarinec G, Jacobs S, Morimoto Y, Chock M, Grandinetti A, Kolonel LN. Disparity in diabetes risk across Native Hawaiians and different Asian groups: the multiethnic cohort. *Asia Pac J Public Health*. 2015;27(4):375-384.

19. Lee JA, Liu CF, Sales AE. Racial and ethnic differences in diabetes care and health care use and costs. *Prev Chronic Dis*. 2006;3(3):A85.

20. Yarboro TL. Emergency room use by patients from the family practice of a black physician. *J Natl Med Assoc*. 1990;82(2):93-97.

21. Mier N, Wang X, Smith ML, et al. Factors influencing health care utilization in older Hispanics with diabetes along the Texas-Mexico border. *Popul Health Manag*. 2012;15(3):149-156.

22. Ashktorab H, Kupfer SS, Brim H, Carethers JM. Racial Disparity in Gastrointestinal Cancer Risk. *Gastroenterology*. 2017;153(4):910-923.

23. Kolonel LN, Henderson BE, Hankin JH, et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. *Am J Epidemiol*. 2000;151(4):346-357.

24. Setiawan VW, Virnig BA, Porcel J, et al. Linking data from the Multiethnic Cohort Study to Medicare data: linkage results and application to chronic disease research. *Am J Epidemiol*. 2015;181(11):917-919.

25. Henry SA, Prizment AE, Anderson KE. Duration of diabetes and pancreatic cancer in a case-control study in the Midwest and the Iowa Women's Health Study (IWHS) cohort. *JOP*. 2013;14(3):243-249.

26. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *CA Cancer J Clin*. 2010;60(4):207-221.

27. Malka D, Hammel P, Maire F, et al. Risk of pancreatic adenocarcinoma in chronic pancreatitis. *Gut*. 2002;51(6):849-852.

28. Li D. Diabetes and pancreatic cancer. *Mol Carcinog*. 2012;51(1):64-74.

29. Gomez-Rubio P, Rosato V, Márquez M, et al. A systems approach identifies time-dependent associations of multimorbidities with pancreatic cancer risk. *Ann Oncol*. 2017;28(7):1618-1624.

30. Office of Hawaiian Affairs Research Demography. *Native Hawaiian Health Fact Sheet 2017*. Honolulu, HI2017.

31. Yadav D, Lowenfels AB. The epidemiology of pancreaticitis and pancreatic cancer. *Gastroenterology*. 2013;144(6):1252-1261.

32. Huang BZ, Stram DO, Le Marchand L, et al. Interethnic differences in pancreatic cancer incidence and risk factors: The Multiethnic Cohort. *Cancer Med*. 2019;8(7):3592-3603.

33. Hawaii Tumor Registry of the University of Hawaii Cancer Center. In.

34. Liu L, Zhang J, Deapen D, et al. Differences in Pancreatic Cancer Incidence Rates and Temporal Trends Across Asian Subpopulations in California (1988-2015). *Pancreas*. 2019;48(7):931-933.

35. Zhang P, Li H, Tan X, Chen L, Wang S. Association of metformin use with cancer incidence and mortality: a meta-analysis. *Cancer Epidemiol*. 2013;37(3):207-218.

36. Karlstad O, Starup-Linde J, Vestergaard P, et al. Use of insulin and insulin analogs and risk of cancer - systematic review and meta-analysis of observational studies. *Curr Drug Saf*. 2013;8(5):333-348.

37. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence*. 2016;10:1299-1307.
Table 1: Descriptive Characteristics of Cases and Controls

| Characteristics                                      | Cases (N=433) | Controls (N=1,728) |
|-----------------------------------------------------|--------------|-------------------|
|                                                      | No. (%)      | No. (%)           |
| Age at cohort entry*, y                             |              |                   |
| <60                                                 | 116 (26.8)   | 463 (26.8)        |
| 60-64                                               | 89 (20.6)    | 360 (20.8)        |
| 65-69                                               | 127 (29.3)   | 526 (30.4)        |
| 70-74                                               | 89 (20.6)    | 342 (19.8)        |
| ≥75                                                 | 12 (2.8)     | 37 (2.1)          |
| Sex*                                                |              |                   |
| Male                                                | 205 (47.3)   | 820 (47.5)        |
| Female                                              | 228 (52.7)   | 908 (52.6)        |
| Race/ethnicity*                                     |              |                   |
| African American                                    | 62 (14.3)    | 248 (14.4)        |
| Native Hawaiian                                     | 40 (9.2)     | 156 (9.0)         |
| Japanese American                                   | 188 (43.4)   | 752 (43.5)        |
| Latino                                              | 60 (13.9)    | 240 (13.9)        |
| White                                               | 83 (19.2)    | 332 (19.2)        |
| Educational attainment                             |              |                   |
| High school or less                                 | 199 (46.0)   | 796 (46.1)        |
| Vocational/Some college                             | 128 (29.6)   | 471 (27.3)        |
| College or higher                                   | 106 (24.4)   | 461 (26.7)        |
| Neighborhood SES, quintiles                         |              |                   |
| 1 (low)                                             | 82 (18.9)    | 292 (16.9)        |
| 2                                                   | 64 (14.8)    | 210 (12.2)        |
| 3                                                   | 76 (17.6)    | 306 (17.7)        |
| 4                                                   | 82 (18.9)    | 259 (15.0)        |
| 5 (high)                                            | 115 (26.6)   | 516 (29.9)        |
| Missing                                             | 14 (3.2)     | 145 (8.4)         |
| Health behaviors                                    |              |                   |
| Alcohol intake (g/day)                              |              |                   |
| <24                                                 | 383 (88.5)   | 1547 (89.5)       |
| ≥24                                                 | 50 (11.6)    | 181 (10.5)        |
| Smoking status                                      |              |                   |
| Never                                               | 198 (45.7)   | 824 (47.7)        |
| Former                                              | 167 (38.6)   | 704 (40.7)        |
| Current                                             | 68 (15.7)    | 200 (11.6)        |
| Any vigorous physical activity (yes)                | 89 (20.6)    | 386 (22.3)        |
| Clinical factors and comorbid conditions            |              |                   |
| Body mass index (kg/m²)                             |              |                   |
| <25                                                 | 181 (41.8)   | 796 (46.1)        |
| 25-29.9                                             | 181 (41.8)   | 679 (39.3)        |
| ≥30                                                 | 71 (16.4)    | 253 (14.6)        |
| Congestive heart failure                            | 57 (13.2)    | 182 (10.5)        |
| Chronic obstructive pulmonary disease               | 90 (20.8)    | 218 (12.6)        |
| Dementia                                            | 24 (5.5)     | 124 (7.2)         |
| Paralysis (Hemiplegia or paraplegia)                | 11 (2.5)     | 23 (1.3)          |
| Mild liver disease                                  | 7 (1.6)      | 19 (1.1)          |
| Moderate/severe liver disease                       | 6 (1.4)      | 7 (0.4)           |
| Peptic ulcer disease                                | 15 (3.5)     | 33 (1.9)          |
| Rheumatologic disease                               | 22 (5.1)     | 56 (3.2)          |
| Cancer prognostic factors                           |              |                   |
| Pancreatic cancer stage at diagnosis                |              |                   |
| Localized                                           | 40 (9.2)     |                   |
| Regional                                            | 131 (30.3)   |                   |
| Metastatic                                          | 196 (45.3)   |                   |
| Age at diagnosis, y | Unknown/not specified | 66 (15.2) |  |
|-------------------|----------------------|-----------|---|
| 67-69             | 38 (8.8)             |           | -|
| 70-74             | 90 (20.8)            |           | -|
| 75-79             | 112 (25.9)           |           | -|
| 80-84             | 111 (25.6)           |           | -|
| ≥85               | 82 (18.9)            |           | -|

*Matching variables: Data from baseline questionnaire (age, sex, race/ethnicity, education, health behaviors, BMI), Medicare claims (diabetes and -related complications, comorbid conditions), and SEER (cancer prognostic factors)*
Table 2. Baseline characteristics by diabetes complications severity index.

| Characteristics          | Diabetes Complications Severity Index (DCS) CASES | Diabetes Complications Severity Index (DCS) CONTROLS |
|--------------------------|---------------------------------|---------------------------------|
|                          | 0  | 1  | 2  | 3  | 4  | 5+ | P*      | 0  | 1  | 2  | 3  | 4  | 5+ | P*     |
|                          | (n=95) | (n=59) | (n=83) | (n=54) | (n=52) | (n=90) |        | (n=669) | (n=236) | (n=289) | (n=167) | (n=172) | (n=195) |        |
| Index age                |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 67-69                    | 16.8 | 10.2 | 8.4 | 5.6 | 3.9 | 4.4 | 0.06 | 10.2 | 8.9 | 9.3 | 4.8 | 5.2 | 4.1 | 0.001 |
| 70-74                    | 16.8 | 18.6 | 28.9 | 24.1 | 28.9 | 13.3 |    | 24.5 | 22.0 | 19.0 | 20.4 | 10.5 | 14.9 |    |
| 75-79                    | 24.2 | 22.0 | 22.9 | 20.4 | 30.8 | 26.7 |    | 24.1 | 29.2 | 23.9 | 27.0 | 20.9 | 25.6 |    |
| 80-84                    | 24.2 | 28.8 | 24.1 | 25.9 | 23.1 | 30.0 |    | 22.3 | 25.4 | 25.6 | 27.0 | 33.7 | 29.2 |    |
| ≥85                      | 17.9 | 20.3 | 15.7 | 24.1 | 13.5 | 25.6 |    | 19.0 | 14.1 | 22.2 | 21.0 | 29.7 | 26.2 |    |
| Sex                      |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Male                     | 39.0 | 47.5 | 43.4 | 50.0 | 67.3 | 46.7 | 0.04 | 46.3 | 43.6 | 49.1 | 43.7 | 51.2 | 53.3 | 0.25    |
| Female                   | 61.1 | 52.5 | 56.6 | 50.0 | 32.7 | 53.3 |    | 53.7 | 56.4 | 50.9 | 56.3 | 48.8 | 46.7 |    |
| Race/ethnicity           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| African American         |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Native                   | 8.4 | 6.8 | 6.0 | 7.4 | 9.6 | 15.6 | 0.001 | 9.0 | 8.5 | 7.6 | 8.4 | 14.0 | 8.2 | 0.001 |
| Hawaiian                 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Japanese                 | 52.6 | 54.2 | 48.2 | 44.4 | 51.9 | 16.7 |    | 46.6 | 50.9 | 48.1 | 46.7 | 35.5 | 21.5 |    |
| Am                       | 4.2 | 15.3 | 10.8 | 18.5 | 17.3 | 21.1 |    | 11.8 | 14.4 | 11.8 | 9.0 | 18.0 | 24.1 |    |
| Latino                   | 25.3 | 11.9 | 24.1 | 13.0 | 9.6 | 22.2 |    | 19.6 | 19.1 | 20.8 | 18.0 | 19.2 | 16.9 |    |
| White                    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Educational              |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| <=High school            |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Some                     | 44.2 | 47.5 | 39.8 | 38.9 | 50.0 | 54.4 | 0.40 | 42.3 | 40.7 | 49.8 | 52.7 | 52.3 | 48.7 | 0.03    |
| College                  | 28.4 | 23.7 | 31.3 | 33.3 | 34.6 | 27.8 |    | 28.7 | 32.6 | 23.2 | 19.2 | 26.2 | 29.7 |    |
| College or higher        | 27.4 | 27.1 | 28.9 | 27.8 | 15.4 | 17.8 |    | 28.7 | 25.9 | 27.0 | 27.5 | 20.4 | 21.0 |    |
| Missing                  | 0 | 1.7 | 0 | 0 | 0 | 0 |    | 0.3 | 0.9 | 0 | 0.6 | 1.2 | 0.5 |    |
| Neighborhood SES, Quintiles |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 1 (low)                  | 17.9 | 20.3 | 13.3 | 18.5 | 13.5 | 27.8 | 0.67 | 14.4 | 14.4 | 15.9 | 14.4 | 22.1 | 27.7 | 0.001 |
| 2                        | 16.8 | 6.8 | 19.3 | 16.7 | 17.3 | 11.1 |    | 10.8 | 12.7 | 11.1 | 11.4 | 16.3 | 14.9 |    |
| 3                        | 14.7 | 17.0 | 13.3 | 22.2 | 25.0 | 17.8 |    | 17.8 | 13.1 | 17.3 | 25.2 | 19.2 | 15.9 |    |
| 4                        | 14.7 | 23.7 | 25.3 | 14.8 | 17.3 | 17.8 |    | 16.4 | 16.1 | 18.0 | 13.2 | 7.6 | 12.3 |    |
| 5 (High)                 | 31.6 | 28.8 | 26.5 | 24.1 | 23.1 | 23.3 |    | 32.9 | 33.9 | 29.4 | 28.7 | 26.7 | 19.0 |    |
| Missing Health behaviors | 4.2 | 3.4 | 2.4 | 3.7 | 3.9 | 2.2 |
|-------------------------|-----|-----|-----|-----|-----|-----|
| Alcohol intake (g/day)  |     |     |     |     |     |     |
| <24                     | 91.6| 86.4| 91.6| 85.2| 86.5| 86.7|
| ≥24                     | 8.4 | 13.6| 8.4 | 14.8| 13.5| 13.3|
| Smoking status          |     |     |     |     |     |     |
| Never                   | 46.3| 44.1| 47.0| 51.9| 38.5| 45.6|
| Former                  | 42.1| 40.7| 45.8| 20.4| 44.2| 34.4|
| Current                 | 11.6| 15.3| 7.2 | 27.8| 17.1| 20.0|
| Any vigorous physical activity |     |     |     |     |     |     |
| No                      | 72.6| 88.1| 81.9| 79.6| 75.0| 81.1|
| Yes                     | 27.4| 11.9| 18.1| 20.4| 25.0| 18.9|
| Clinical factors and comorbid conditions |     |     |     |     |     |     |
| BMI (kg/m²)             |     |     |     |     |     |     |
| <25                     | 54.7| 45.8| 38.6| 46.3| 25.0| 35.6|
| 25-29.9                 | 35.8| 42.4| 44.6| 38.9| 53.9| 40.0|
| ≥30                     | 9.5 | 11.9| 16.9| 14.8| 21.2| 24.4|
| COPD                    |     |     |     |     |     |     |
| No                      | 87.4| 81.4| 84.3| 81.5| 71.1| 67.8|
| Yes                     | 12.6| 18.6| 15.7| 18.5| 28.9| 32.2|
| Dementia                |     |     |     |     |     |     |
| No                      | 97.9| 98.3| 95.2| 92.6| 96.1| 87.8|
| Yes                     | 2.1 | 1.7 | 4.8 | 7.4 | 3.9 | 12.2|
| Rheumatologic disease   |     |     |     |     |     |     |
| No                      | 95.8| 96.6| 95.2| 100 | 98.2| 87.8|
| Yes                     | 4.2 | 3.4 | 4.8 | 0   | 1.9 | 12.2|

|                 | 7.8 | 9.8 | 8.3 | 7.2 | 8.1 | 10.3 |
|-----------------|-----|-----|-----|-----|-----|------|
|                 | 0.71| 0.33| 0.04| 0.06| 0.26| 0.32 |

*Copied Chi-squared test.
Table 3. Descriptive characteristics of diabetes and diabetes-related complications, by race/ethnicity

| Chronic Condition | CASES | | | | | | CONTROLS | | | | | |
|-------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|                   | Total | African American | Native Hawaiian | Japanese American | Latino | White | P* | Total | African American | Native Hawaiian | Japanese American | Latino | White | P* |
|                   | %     | %     | %     | %     | %     | %     |     | %     | %     | %     | %     | %     | %     |     |     |     |
| Diabetes          | 45.5  | 50.0  | 45.0  | 45.7  | 58.3  | 32.5  | 0.001 | 31.4  | 43.7  | 39.1  | 32.9  | 37.1  | 17.8  | 0.001 |
| Diabetes-related complications | | | | | | | | | | | | | | | | |
| Retinopathy       | 16.4  | 16.1  | 22.5  | 14.4  | 23.3  | 13.3  | 0.36  | 13.7  | 16.5  | 14.1  | 12.9  | 12.1  | 14.2  | 0.58  |
| Neuropathy        | 19.2  | 22.6  | 25.0  | 8.5   | 43.3  | 20.5  | 0.001 | 13.4  | 19.0  | 12.8  | 10.1  | 17.5  | 14.2  | 0.002 |
| Nephropathy       | 31.2  | 38.7  | 47.5  | 25.0  | 40.0  | 25.3  | 0.009 | 18.3  | 23.4  | 25.0  | 15.4  | 25.4  | 12.7  | 0.002 |
| Cerebrovascular   | 21.7  | 35.5  | 22.5  | 14.4  | 28.3  | 22.9  | 0.006 | 17.6  | 24.2  | 14.1  | 14.4  | 23.3  | 17.5  | 0.006 |
| Cardiovascular    | 61.2  | 74.2  | 62.5  | 54.8  | 71.7  | 57.8  | 0.03  | 43.9  | 49.6  | 46.8  | 38.0  | 53.8  | 44.3  | 0.001 |
| Peripheral        | 18.5  | 32.3  | 17.5  | 9.0   | 36.7  | 16.9  | 0.001 | 12.0  | 25.4  | 10.9  | 6.1   | 20.0  | 10.2  | 0.001 |
| Vascular disease  |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
| Metabolic         | 3.5   | 1.6   | 5.0   | 3.7   | 3.3   | 3.6   | 0.92  | 0.5   | 0.4   | 1.3   | 0.3   | 0.8   | 0.3   | 0.43  |
| Diabetes Complications Severity Index (DCSI) | | | | | | | | | | | | | | | | 0.001 |
| 0                 | 21.9  | 14.5  | 20.0  | 26.6  | 6.7   | 28.9  | 0.001 | 38.7  | 35.1  | 38.5  | 41.5  | 32.9  | 39.5  | 0.001 |
| 1                 | 13.6  | 11.3  | 10.0  | 17.0  | 15.0  | 8.4   |       | 13.7  | 6.9   | 12.8  | 16.0  | 14.2  | 13.6  |       |
| 2                 | 19.2  | 14.5  | 12.5  | 21.3  | 15.0  | 24.1  |       | 16.7  | 13.7  | 14.1  | 18.5  | 14.2  | 18.1  |       |
| 3                 | 12.5  | 14.5  | 10.0  | 12.8  | 16.7  | 8.4   |       | 9.7   | 12.1  | 9.0   | 10.4  | 6.3   | 9.0   |       |
| 4                 | 12.0  | 9.7   | 12.5  | 14.4  | 15.0  | 6.0   |       | 10.0  | 9.3   | 15.4  | 8.1   | 12.9  | 9.9   |       |
| 5+                | 20.8  | 35.5  | 35.0  | 8.0   | 31.7  | 24.1  |       | 11.2  | 23.0  | 10.3  | 5.6   | 19.6  | 9.9   |       |

* Two-sided Chi-squared test of association between race/ethnicity and each diabetes-related complication and DCSI.
Table 4: Relative risk of pancreatic cancer in relation to the presence of diabetes and diabetes-related complications compared to the absence of each condition.

| Chronic Condition                        | No. of cases/No. of controls | OR* (95% CI)     | OR† (95% CI)     |
|------------------------------------------|------------------------------|-----------------|-----------------|
| Diabetes (yes vs. no)                    | 197/524                      | 1.46 (1.12-1.88) | 1.48 (1.14-1.91) |
| Diabetes-related complications           |                              |                 |                 |
| Retinopathy (yes vs. no)                 | 71/236                       | 0.82 (0.59-1.13) | 0.85 (0.61-1.19) |
| Neuropathy (yes vs. no)                  | 83/232                       | 1.14 (0.84-1.55) | 1.09 (0.79-1.49) |
| Nephropathy (yes vs. no)                 | 135/316                      | 1.72 (1.30-2.27) | 1.75 (1.32-2.33) |
| Cerebrovascular (yes vs. no)             | 94/304                       | 0.92 (0.69-1.24) | 0.93 (0.68-1.27) |
| Cardiovascular (yes vs. no)              | 265/758                      | 1.80 (1.40-2.30) | 1.88 (1.45-2.44) |
| Peripheral vascular disease (yes vs. no) | 80/209                       | 1.08 (0.77-1.52) | 1.11 (0.79-1.57) |
| Metabolic (yes vs. no)                   | 15/8                         | 5.84 (2.26-15.09)| 6.61 (2.49-17.50)|

*Conditional logistic regression model adjusted for education, neighborhood-level SES, alcohol intake, smoking status, any vigorous physical activity and BMI and matched factors (age, race, sex) were used to define strata.
†Conditional logistic regression model adjusted for education, neighborhood-level SES, alcohol intake, smoking status, any vigorous physical activity, BMI, diabetes, and other comorbid conditions and matched factors (age, race, sex) were used to define strata.
Table 5: Relative risk of pancreatic cancer and diabetes complications severity index (DCSI), by diabetes status

| Risk factor | No. of cases/ No. of controls | OR† (95% CI) | OR* (95% CI) |
|-------------|-------------------------------|-------------|-------------|
| Total Cohort (n=2161) | | | |
| DCSI (continuous) | -- | 1.20 (1.14-1.26) | 1.18 (1.11-1.25) |
| DCSI (categorical) | | | |
| 0 | 95/669 | 1.00 (Reference) | 1.00 (Reference) |
| 1 | 59/236 | 1.77 (1.24-2.54) | 1.61 (1.11-2.33) |
| 2 | 83/289 | 2.10 (1.51-2.93) | 1.94 (1.38-2.74) |
| 3 | 54/167 | 2.41 (1.65-3.54) | 2.26 (1.52-3.37) |
| 4+ | 142/367 | 3.02 (2.22-4.11) | 2.59 (1.82-3.69) |
| Without diabetes (n=1422) | | | |
| DCSI (continuous) | -- | 1.18 (1.10-1.27) | 1.23 (1.11-1.36) |
| With diabetes (n=739) | | | |
| DCSI (continuous) | -- | 1.12 (1.05-1.19) | 1.22 (1.09-1.36) |

† Conditional logistic regression adjusted for matched factors (age, race, sex) were used to define strata.
*Conditional logistic regression adjusted for education, neighborhood-level SES, alcohol intake, smoking status, any vigorous physical activity, BMI, diabetes and other comorbid conditions and matched factors (age, race, sex) were used to define strata.