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Int J Cancer. Author manuscript; available in PMC 2024 July 20.

Published in final edited form as:

Int J Cancer. 2023 January 15; 152(2): 172–182. doi:10.1002/ijc.34235.

Autoimmune conditions and pancreatic cancer risk in older American adults

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Abstract

Pancreatic cancer (PC) is highly fatal, and its incidence is increasing in the United States. Population-based registry studies suggest associations between a few autoimmune conditions and PC risk, albeit based on a relatively small number of cases. We conducted a population-based, nested case-control study to examine the association between autoimmune conditions and PC risk within the Surveillance, Epidemiology, and End Results Program (SEER)-Medicare population. Incident primary malignant PC cases (n=80,074) were adults ≥ 66 years and diagnosed between 1992 and 2015. Controls (n=320,296) were alive at the time cases were diagnosed and frequency-matched to cases (4:1 ratio) by age, sex, and year of diagnosis. We used multivariable-adjusted, unconditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for 45 autoimmune conditions identified from Medicare claims. Eight autoimmune conditions including ankylosing spondylitis (OR = 1.45; 95% CI: 1.14–1.84), Graves' disease (OR = 1.18; 95% CI: 1.03–1.34), localized scleroderma (OR = 1.27; 95% CI: 1.06–1.52), pernicious anemia (OR = 1.08; 95% CI: 1.02–1.14), primary sclerosing cholangitis (OR = 1.37; 95% CI: 1.18–1.59), pure red cell aplasia (OR = 1.31; 95% CI: 1.16–1.47), type 1 diabetes (OR = 1.11; 95% CI: 1.07–1.15), and ulcerative colitis (OR = 1.18; 95% CI: 1.07–1.31) were associated with increased PC risk (false discovery rate-adjusted *P* values < 0.10). In subtype analyses, these conditions were associated with pancreatic ductal adenocarcinoma, whereas only ulcerative colitis was associated

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Conceptualization: RSS. Data curation: SJS, MJB, RSS. Formal statistical analysis: RMP, MJB. Funding acquisition: RSS. Investigation: FY, RMP, SJS, SA, MJB, JK, RSS. Methodology: RMP, RSS. Project administration: RSS. Resources: RSS. Supervision: RMP, RSS. Writing — original draft: FY, RSS. Writing —review & editing: FY, RMP, SJS, SA, MJB, JK, RSS. All authors read, revised, and approved the final draft. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

Conflict of Interest

The authors disclose no potential conflict of interest related to this study.

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The content of the article is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Ethics Statement

Research using the SEER-Medicare data is deemed exempt by the National Institutes of Health Office of Human Subjects Research Protection.

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with pancreatic neuroendocrine tumors. Our results support the hypothesis that autoimmune conditions may play a role in PC development.

Keywords

pancreatic cancer; autoimmune conditions; SEER-Medicare data; epidemiology

Introduction

The incidence of pancreatic cancer (PC) has been increasing in the US and worldwide.[1, 2] Pancreatic ductal adenocarcinoma (PDAC) and pancreatic neuroendocrine tumors (PNETs) are the two most common PC subtypes. Cigarette smoking, diabetes mellitus, chronic pancreatitis and excess weight are known risk factors for PDAC.[3] Risk factors for PNETs are largely unknown beyond rare inherited genetic syndromes.[4]

Autoimmune conditions are characterized by immune dysregulation and have been associated with increased risks of gastrointestinal tract cancers in registry-based studies.[5–18] However, current evidence on the associations of autoimmune conditions, particularly Crohn's disease,[6, 7, 10, 16, 17] ulcerative colitis,[7, 8, 10, 16, 17, 19] and systemic lupus erythematosus,[10, 15] and celiac disease[10–12, 16] have been inconsistent. Many of these studies have insufficient power to detect associations due to the relatively low prevalence of autoimmune conditions and PC in the general population. Previously, we showed that joint effects of common variants in genomic regions containing susceptibility loci for Crohn's disease and ulcerative colitis were associated with PDAC, suggesting a shared genetic architecture between the diseases.[20]

In this study, we examined associations between autoimmune conditions and PC risk in a large population-based, nested case-control study of older adults within the US Surveillance, Epidemiology, and End Results Program (SEER)-Medicare linked data. We hypothesize that autoimmune conditions are associated with the risk of PC.

Methods

Data sources

We conducted a population-based, nested case-control study within the SEER-18 Medicare database.[21] Briefly, the National Cancer Institute's SEER Program collects information on cancer incidence, mortality, and survival from population-based cancer registries which currently cover approximately 35% of the US population.[22] Medicare is a federally funded health insurance program that provides coverage for 97% of the US population aged 65 years or older and younger people with end-stage renal disease and disabilities. All Medicare beneficiaries are enrolled in Part A benefits which includes inpatient hospital, skilled-nursing facility, hospice and some home health care. Ninety-six percent of those enrolled in Part A also subscribe to Part B which covers physician and outpatient services.

The SEER-Medicare is an electronic linkage database in which SEER cancer registries data are matched to Medicare beneficiaries and claims.[23] Approximately 95% of individuals aged

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65 or older in the SEER database are linked to the Medicare enrollment file. Research using the SEER-Medicare data is deemed exempt by the National Institutes of Health Office of Human Subjects Research Protection.

Case ascertainment and selection of controls

PC cases were defined as participants with primary malignant disease [first and later (i.e., PC diagnosed after diagnosis of a primary malignant neoplasm at sites other than the pancreas) primary; International Classification of Disease for Oncology, ICD-O codes C25.0-C25.9 with malignant code 3], identified in the SEER-Medicare Patient Entitlement Diagnosis Summary File (PEDSF) between January 1, 1992 and December 31, 2015. PC diagnosed at autopsy or by death certificates only were excluded because they differed from cancers diagnosed clinically.[24] Cases were required to have at least 13 months of Medicare Part A and B, non-health maintenance organization (HMO) coverage, making the minimum age at PC diagnosis 66 years. Cases were also required to have at least one Medicare claim [Medicare Provider Analysis and Review (MedPAR), National Claims History (NCH), or Outpatient] more than 12 months prior to PC diagnosis to ensure that they utilized Medicare benefits. Cases over the age of 99 were excluded (online supplementary figure 1). We used the ICD-O morphological classification to create mutually exclusive PC subgroups for PDAC (8000, 8010, 8140, 8144, 8145, 8255, 8440, 8450, 8453, 8460, 8470, 8471, 8480, 8481, 8490, 8500, 8503, 8504, 8507, 8510, 8514, 8521, 8523, 8560, 8570) and PNETs (8240, 8243–8245,8150, 8246,8151–8153, 8155).

Controls were randomly selected in a 4:1 ratio for each first primary case from a 5% representative random sample of Medicare-enrolled beneficiaries without cancer residing in the geographic region covered by SEER, or from a 5% random sample of participants from the SEER-Medicare PEDSF. Controls were alive and either free of cancer or PC (for first primary or later primary, respectively) as of July 1 of the calendar year that the case was diagnosed, and frequency-matched to the cases by age (66–69, 70–74, 75–79, 80–84, 85–89, 90–94, and 95–99), sex, and calendar year of diagnosis (±1 year). Controls were subject to the same exclusion criteria as the cases.

Ascertainment of autoimmune conditions and other exposures

Forty-five autoimmune conditions identified by International Classification of Diseases 9th edition (ICD-9) codes from Medicare claims were included in this study (online supplementary table 1). A diagnosis of autoimmune condition was defined as having a minimum of one inpatient claim (MeDPAR) or two physician/outpatient (NCH or Outpatient) claims at least 30 days apart. We required autoimmune conditions be diagnosed at least 12 months before cancer diagnosis/control selection to minimize surveillance bias and reverse causation.

We used ICD-9 codes from Medicare claims for certain medical conditions as surrogate measures for smoking and heavy alcohol use. Subjects with chronic obstructive pulmonary disorder (COPD; except asthma, 490, 491, 492, 494, 495, or 496), personal history of tobacco use (V15.82) or non-dependent tobacco use disorder (305.1) were considered smokers and those with any alcohol-induced liver disorders (571.0, 571.1, 571.2, 571.3),

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alcohol-induced psychiatric or neurologic disorders (291), alcohol intoxication (303), non-dependent alcohol abuse (305), or a personal history of alcoholism (V11.3) were classified as heavy alcohol users. Type 2 diabetes (250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92, 790.2), overweight/obesity (278.0, 278.01, 278.02, 278.1, V77.8, 783.1, 278.00, 278.01), and chronic/acute pancreatitis (577.0, 577.1) diagnoses were also determined with ICD-9 codes.

Statistical analysis

We used unconditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between autoimmune conditions and PC. Models were adjusted for age category (66–69, 70–74, 75–79, 80–84, 85–89, 90–99 years), sex, calendar year category of PC diagnosis/selection (1992–2000, 2001–2005, 2006–2009, 2010–2015), race/ethnicity (non-Hispanic White, non-Hispanic Black, Asian/Pacific Islander, Hispanic, other/unknown), geographic region (SEER registry), Medicaid eligibility (ever, never), average number of physician visits per 6 months in the 5 years before diagnosis/selection (quintiles in controls), average duration of Medicare part A, B, non-HMO coverage (quintiles in controls), Medicare low-income subsidy (ever, never, unknown), overweight/obesity (ever, never diagnosed), smoking behavior-related diagnoses (ever, never diagnosed), COPD (ever, never diagnosed), alcohol-related diagnoses (ever, never diagnosed), type 2 diabetes mellitus (ever, never diagnosed), chronic or acute pancreatitis (ever, never diagnosed).

We conducted exploratory stratified analyses by PC subtypes (PDAC, PNETs for the most significant autoimmune conditions), sex, age (< 75 years, ≥ 75 years), and race (non-Hispanic White, non-Hispanic Black). Race of other categories were not included in the analysis due to limited sample size. We fitted a two-stage hierarchical logistic regression model (online supplementary methods) separately to three groups (“primary gastrointestinal”, “secondary gastrointestinal-associated”, and “not gastrointestinal-associated”) to assess the combined effects of conditions within the same group.[25] The hierarchical models also account for correlations due to multiple autoimmune conditions occurring in the same individual and thus improve the accuracy of risk estimates. To account for the long duration of pancreatic cancer development and surveillance bias due to autoimmune disease diagnosis, we also conducted a sensitivity analysis to examine the associations of autoimmune conditions with all primary PC among participants whose cancer diagnosis/control selection was at least five years after autoimmune condition diagnosis. All statistical tests were two-sided. We considered a false discovery rate (FDR)-adjusted P (P_{FDR}) value < 0.10 statistically significant.[26] Analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Our study included 80,074 incident PC cases and 320,296 population-based controls (Table 1). Among the PC cases, 61,081 (76.3%) were first primary and 18,993 (23.7%) were later primary. Compared with controls, PC cases were more likely to be non-Hispanic Black, have

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longer Medicare Part A, B, non-HMO coverage, visit physicians more frequently six months prior to diagnosis/selection, and have diagnoses of overweight/obesity, COPD, acute/chronic pancreatitis, type 2 diabetes, and smoking behavior- and alcohol-related comorbidities. Compared with first primary cases, later primary cases were more likely to be older, male, non-Hispanic White, have longer Medicare Part A, B, non-HMO coverage and more physician visits six months prior to diagnosis, and have diagnoses of overweight/obesity, COPD, acute/chronic pancreatitis, type 2 diabetes, and smoking behavior- or alcohol-related comorbidities.

Eight autoimmune conditions were significantly associated with an elevated risk of all PC at P_{FDR} value < 0.10 (Table 2): ankylosing spondylitis (OR = 1.45; 95% CI: 1.14–1.84), Graves' disease (OR = 1.18; 95% CI: 1.03–1.34), localized scleroderma (OR = 1.27; 95% CI: 1.06–1.52), pernicious anemia (OR = 1.08; 95% CI: 1.02–1.14), primary sclerosing cholangitis (OR = 1.37; 95% CI: 1.18–1.59), pure red cell aplasia (OR = 1.31; 95% CI: 1.16–1.47), type 1 diabetes (OR = 1.11; 95% CI: 1.07–1.15), and ulcerative colitis (OR = 1.18; 95% CI: 1.07–1.31). We also observed a suggestive positive association for discoid lupus erythematosus (OR = 1.30; 95% CI: 1.03–1.64; P_{FDR} value = 0.12). These associations were similar in magnitude or in the same direction for first and later primary PC except for pure red cell aplasia which was only associated with later primary PC (OR = 2.00; 95% CI: 1.68–2.37). In addition, aplastic anemia (OR = 2.09; 95% CI: 1.21–3.61) was positively associated with later primary PC, whereas rheumatoid arthritis (OR = 0.89; 95% CI: 0.81–0.97) was inversely associated. Associations with PC were generally similar in stratified analyses, although stronger associations were present in women compared with men for Graves' disease; in participants ≥ 75 years old compared with < 75 years old for localized scleroderma, primary sclerosing cholangitis, and pure red cell aplasia; and in non-Hispanic White compared with non-Hispanic Black for pernicious anemia and pure red cell aplasia (online supplementary tables 2–4). In hierarchical models that mutually adjusted for conditions in the same group, the eight top autoimmune conditions remained significantly associated with PC (online supplementary table 5). Among participants diagnosed with autoimmune conditions five years or more before PC diagnosis (online supplementary table 6, n=56,624 cases and 220,531 controls), Graves' disease (OR =1.33; 95% CI: 1.10–1.62), pure red cell aplasia (OR = 1.45; 95% CI: 1.19–1.77), type 1 diabetes (OR = 1.15; 95% CI: 1.10–1.21), and ulcerative colitis (OR = 1.22; 95% CI: 1.05–1.43) remained significant after adjusting for multiple comparison, whereas the associations for ankylosing spondylitis (OR = 1.61; 95% CI: 1.11–2.35) and localized scleroderma (OR = 1.40; 95% CI: 1.07–1.83) were positive however not at P_{FDR} value < 0.10. The associations for pernicious anemia (OR = 1.06; 95% CI: 0.97–1.15) and primary sclerosing cholangitis (OR = 0.96; 95% CI: 0.69–1.34) became non-significant.

Table 3 shows the results for the eight most significant, PC-associated autoimmune conditions (P_{FDR} value < 0.10) stratified by the PDAC and PNET subtypes. Ankylosing spondylitis (OR = 1.42; 95% CI: 1.12–1.81), Graves' disease (OR = 1.18; 95% CI: 1.04–1.35), localized scleroderma (OR = 1.24; 95% CI: 1.03–1.48), pernicious anemia (OR = 1.08; 95% CI: 1.02–1.14), primary sclerosing cholangitis (OR = 1.38; 95% CI: 1.19–1.60), pure red cell aplasia (OR = 1.33; 95% CI: 1.18–1.49), type 1 diabetes (OR = 1.11; 95% CI: 1.07–1.15), and ulcerative colitis (OR = 1.16; 95% CI: 1.05–1.29) were significantly

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associated with PDAC. Only ulcerative colitis was associated with PNETs (OR = 1.78; 95% CI: 1.17–2.70).

Discussion

In this largest, most comprehensive study to date, prior diagnoses of ankylosing spondylitis, Graves' disease, localized scleroderma, pernicious anemia, primary sclerosing cholangitis, pure red cell aplasia, type 1 diabetes, and ulcerative colitis were significantly associated with 8–45% increased risk of primary PC. The associations were in the same direction for first and later primary PC except for pure red cell aplasia, where a positive association was only present with risk of later primary. In analyses stratified by PC histological subtypes, the eight autoimmune conditions were similarly associated with an elevated PDAC risk, whereas only ulcerative colitis was significantly associated with 78% increased PNETs risk.

The positive associations we observe for ankylosing spondylitis, Graves' disease, and localized scleroderma with overall PC and PDAC, and for ulcerative colitis with PNETs are novel. Studies based on US Veterans Affairs hospital admissions or registry-based cohort studies in Sweden and Taiwan have not observed significant associations for ankylosing spondylitis, Graves' disease, or localized scleroderma and PC, although these studies included small numbers of PC cases (N = 1–24).[10, 27–29] Ankylosing spondylitis has been significantly associated with cancer risk of the ampulla of Vater,[14] which connects pancreatic ducts to the small intestine. Methimazole, an antithyroid medication used to treat Graves' disease, has been shown to increase the risk of acute pancreatitis and might contribute to the association we observe.[30] To the best of our knowledge, no previous study has examined the association of ulcerative colitis with PNETs. One population-based study based on the Dutch Pathology Registry reported a higher prevalence of colonic neuroendocrine tumors among inflammatory bowel disease patients compared with the general population.[31] Future observational and animal studies are needed to replicate our results and elucidate plausible disease mechanisms.

Previous studies on the association of primary sclerosing cholangitis with PC risk are limited. Two Swedish studies have reported 8 to 14-fold elevated risk for primary sclerosing cholangitis, albeit based on ≤ 20 PC cases.[9, 18] The observed association may be partially explained by the misdiagnosis of PC with extrahepatic cholangiocarcinoma,[32] a malignancy which is strongly associated with primary sclerosing cholangitis.[14] However, this is unlikely a limitation of our study because cancer diagnoses from SEER registries are of the highest data quality[33] and our study included a large number of PC cases. Current evidence on the association of ulcerative colitis with PC risk is inconsistent. Scandinavian registry-based studies have observed significant 35–45% elevated PC risk associated with ulcerative colitis diagnosis.[7, 8] One case-control study among 1,705 PC cases and 1,084 controls from PanGenEU (European Study into Digestive Illnesses and Genetics) study reported a null association between ulcerative colitis and PC risk,[19] however was based on 15 cases and 16 controls reporting ulcerative colitis. A more recent case-control study in the SEER-Medicare population reported a suggestive positive association between ulcerative colitis and first primary PC risk (OR = 1.12; 95% CI: 0.99–1.27).[17] In contrast to our study, this earlier SEER-Medicare study did not include later primary PC and did not adjust for overweight/

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obesity, smoking behavior-related diagnoses, alcohol-related diagnoses, type 2 diabetes mellitus, and acute/chronic pancreatitis. Our findings are also consistent with our earlier investigation using genome-wide association study (GWAS) data which suggested that ulcerative colitis shared genetic architecture with PDAC.[20] We did not observe a statistically significant association of genomic regions for primary sclerosing cholangitis (***P* value = 0.078) with PDAC in our earlier analysis,** partly due to few established GWAS loci for primary sclerosing cholangitis.[20] Patients with inflammatory bowel diseases, particularly ulcerative colitis, are known to have a higher prevalence of primary sclerosing cholangitis,[34] and it is possible that the positive PC associations observed for both autoimmune conditions could be driven by the same underlying mechanism of carcinogenesis.

Diabetes is a known risk factor for PC, most notably type 2 diabetes related to excess adiposity.[35, 36] Growing evidence suggests type 1 diabetes may be associated with PC.[37, 38] In a meta-analysis based on three cohort and six case-control studies with a total of 39 PC cases, patients diagnosed with type 1 or young-onset diabetes before the age of 40 had a two-fold increased PC risk compared with non-diabetic subjects.[37] A population-based registry study from five European countries including 387 PC cases found statistically significant 1.53- and 1.25-fold elevated PC risks among male and female patients with type 1 diabetes, respectively. The associations were attenuated 10 to 15 years after diabetes diagnosis possibly due to reverse causation.[38] A limitation of these studies is the potential misclassification of diabetes type because type 1 diabetes was frequently defined as having diabetes at a young age without a specific diagnosis.[37, 38] Although we used ICD-9 codes to ascertain type 1 diabetes, diabetes misclassification may still be present in our study.

Findings from previous studies on the association between pernicious anemia and PC are conflicting. Two population-based cohort studies and one case-control study reported null associations between pernicious anemia and PC among hospitalized male US veterans, patients in the Health Improvement Network database of the United Kingdom, and participants of the PanGenEU study.[10, 19, 39] Possible explanations for discrepancies in the reported association between our study and these earlier studies include differences in study design and/or population, sample size, and adjusted covariates in regression models. A Swedish population-based hospital discharge cohort[40] and an earlier population-based, case-control study in the SEER-Medicare population both found significant positive associations between pernicious anemia diagnosis and PC risk,[41] which are consistent with our findings. Pernicious anemia is an autoimmune condition that results from autoantibody-mediated destruction of intrinsic factor-secreting parietal cells, and manifests primarily as vitamin B_{12} deficiency, achlorhydria and subsequent elevated serum gastrin concentration.[42] *In vitro* studies have shown that gastrin stimulates the proliferation and metastasis of human PC cells.[43, 44] Given that our association between pernicious anemia and PC became non-significant when we excluded cases with autoimmune conditions first reported less than five years prior to PC diagnosis, our results might also be explained by reverse causation.

The biological basis for our observed associations is speculative. Most of the autoimmune conditions that we observed significant associations with PC affect the gastrointestinal tract either directly or secondarily. Chronic inflammation and subsequent tissue damage caused by autoimmune conditions, or their therapies may promote tumorigenesis and

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progression through multiple mechanisms, including DNA damage and oncogenic mutations, angiogenesis, antagonizing anti-tumor immunity, cell growth and survival, and enhanced invasion and metastasis.[45] Immunosuppressive treatments for ulcerative colitis and localized scleroderma,[46, 47] hyperglycemia and exogenous insulin treatment related to type 1 diabetes,[38] and tumor-promoting effect of thyroid hormones for Graves' disease could also contribute.[48] The associations of pure red cell aplasia and aplastic anemia with later primary PC risk might be sequelae of the earlier malignancies or cancer therapies, respectively.[49, 50]

Strengths of our study includes large numbers of PC cases which allowed for examination of rare autoimmune conditions and PC subtype analyses. SEER-Medicare is representative of the US population aged 65 years and older.[21] The PC cases were identified through SEER registries, which employs rigorous standards to ensure accuracy of cancer case ascertainment.[33] By using Medicare claims for autoimmune conditions identified more than one year prior to cancer diagnosis instead of self-report, we reduced the likelihood of reverse causation and recall bias.

Our study also has limitations. Since many autoimmune conditions causes symptoms that are associated with pancreatic cancer, surveillance bias could potentially affect the study findings (e.g., fatigue and weight loss caused by Graves' disease and red cell dysplasia could make physicians monitor pancreatic disorders more closely). However, we attempted to minimize surveillance bias by adjusting for the average number of physician visits per 6 months in the 5 years before cancer diagnosis/control selection and excluding autoimmune conditions diagnosed within 12 months of pancreatic cancer diagnosis. Additionally, we conducted a sensitivity analysis in which only autoimmune conditions diagnosed at least 5 years before pancreatic cancer diagnosis were included. Our findings were robust and mostly remained in all these analyses. Given that our study examined the associations of 45 autoimmune conditions with pancreatic cancer risk, some of the significant findings may be due to chance; however, we controlled for multiple comparisons by employing a false discovery rate of < 0.10. Thus, among the 8 findings (or 4 after excluding cancer cases diagnosed within 5 years of autoimmune condition diagnosis), at most 10% could be false positives. Due to the nature of Medicare claims data, some autoimmune conditions (e.g., primary sclerosing cholangitis)[51] and risk factors (e.g., overweight/obesity, smoking and alcohol use) may be under-ascertained, particularly if medical conditions were diagnosed prior to age 66. We applied strict definitions of disease diagnoses (i.e., $\geq$ one inpatient claim or two physician/outpatient claims) to reduce potential misclassification of autoimmune conditions and would expect under-ascertainment to attenuate associations. We used alcohol- and smoking behavior-related disorders and diseases as proxies for heavy drinker and smokers, and thus some residual confounding may be present. Our study lacks complete information on treatments for autoimmune conditions, which could influence cancer risk.[46] Finally, our findings may not be generalizable to younger persons with autoimmune conditions.

In conclusion, results from our large, comprehensive analysis support autoimmune conditions, particularly those that affect gastrointestinal tract either directly or secondarily, are associated with increased PC risk in older US adults. The prevalence of autoimmune conditions is increasing in the US, particularly in older people,[52] and could plausibly be

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contributing to the increasing incidence of PC in addition to other known PC risk factors. Further population and experimental investigations are warranted to confirm our findings and elucidate the mechanisms by which immune dysregulation contributes to pancreatic carcinogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study used the linked SEER-Medicare database. The interpretation and reporting of the SEER-Medicare linkage data are the sole responsibility of the authors. The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement # U58DP003862–01 awarded to the California Department of Public Health. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred. The authors acknowledge the efforts of the National Cancer Institute; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

Funding

This work was supported by the Intramural Research Program of the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Data Availability Statement

The SEER-Medicare data are available to investigators for research purposes. SEER-Medicare data are maintained by the Division of Cancer Control and Population Sciences at the National Cancer Institute, National Institutes of Health. Qualified researchers can apply to obtain SEER-Medicare data for specific research questions at: https://healthcaredelivery.cancer.gov/seermedicare/obtain/requests.html. Further information is available from the corresponding author upon request.

Abbreviations

CI	confidence interval
COPD	chronic obstructive pulmonary disease
FDR	false discovery rate
GWAS	genome wide association study
HMO	health maintenance organization
ICD	International Classification of Diseases

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MedPAR	Medicare Provider Analysis and Review
NCH	National Claims History
OR	odds ratio
PC	pancreatic cancer
PDAC	pancreatic ductal adenocarcinoma
PEDSF	Patient Entitlement Diagnosis Summary File
PNET	pancreatic neuroendocrine tumor
SEER	Surveillance, Epidemiology, and End Results
US	United States

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Novelty and Impact

This large population-based, nested case-control study found that eight autoimmune conditions, ankylosing spondylitis, Graves' disease, localized scleroderma, pernicious anemia, primary sclerosing cholangitis, pure red cell aplasia, type 1 diabetes, and ulcerative colitis were significantly associated with elevated risks of pancreatic cancer overall and pancreatic ductal adenocarcinoma. Ulcerative colitis was significantly associated with pancreatic neuroendocrine tumors. Our results support the role for autoimmunity and immune dysregulation in the etiology of pancreatic cancer.

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Table 1.

Characteristics of SEER-Medicare pancreatic cancer cases and frequency-matched controls[a], 1992–2015.

Characteristics	Control *N* = 320,296	Pancreatic cancer cases		
		First primary *N* = 61,081 (76.3%)	Later primary *N* = 18,993 (23.7%)	All primary *N* = 80,074
Age (years), *n* (%)				
66–69	42,388 (13.2)	8,590 (14.1)	2,007 (10.6)	10,597 (13.2)
70–74	71,148 (22.2)	13,979 (22.9)	3,808 (20.0)	17,787 (22.2)
75–79	75,692 (23.6)	14,253 (23.3)	4,670 (24.6)	18,923 (23.6)
80–84	66,048 (20.6)	12,140 (19.9)	4,372 (23.0)	16,512 (20.6)
85–89	43,496 (13.6)	7,991 (13.1)	2,883 (15.2)	10,874 (13.6)
90–94	17,524 (5.5)	3,357 (5.5)	1,024 (5.4)	4,381 (5.5)
95–99	4000 (1.2)	771 (1.3)	229 (1.2)	1,000 (1.2)
Median (IQR)	77 (72–83)	77 (72–83)	78 (73–84)	78 (72–83)
Sex, *n* (%)				
Male	144,484 (45.1)	26,277 (43.0)	9,844 (51.8)	36,121 (45.1)
Female	175,812 (54.9)	34,804 (57.0)	9,149 (48.2)	43,953 (54.9)
Race, *n* (%)				
White (non-Hispanic)	264,161 (82.5)	49,619 (81.2)	16,171 (85.1)	65,790 (82.2)
Black (non-Hispanic)	23,841 (7.4)	6,179 (10.1)	1,705 (9.0)	7,884 (9.8)
Asian/Pacific Islander	14,483 (4.5)	2,176 (3.6)	442 (2.3)	2,618 (3.3)
Hispanic	7,893 (2.5)	1,227 (2.0)	237 (1.2)	1,464 (1.8)
Other/Unknown	9,918 (3.1)	1,880 (3.1)	438 (2.3)	2,318 (2.9)
Year of diagnosis/selection[b], *n* (%)				
1992–2000	61,352 (19.2)	12,382 (20.3)	2,956 (15.6)	15,338 (19.2)
2001–2005	73,460 (22.9)	14,279 (23.4)	4,086 (21.5)	18,365 (22.9)
2006–2009	71,592 (22.4)	13,537 (22.2)	4,361 (23.0)	17,898 (22.4)
2010–2015	113,892 (35.6)	20,883 (34.2)	7,590 (40.0)	28,473 (35.6)
SEER registry, *n* (%)				
San Francisco	15,050 (4.7)	2,867 (4.7)	943 (5.0)	3,810 (4.8)
Connecticut	23,327 (7.3)	5,009 (8.2)	1,402 (7.4)	6,411 (8.0)
Detroit	24,417 (7.6)	5,494 (9.0)	1,852 (9.8)	7,346 (9.2)

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Characteristics	Control *N* = 320,296	Pancreatic cancer cases		
		First primary *N* = 61,081 (76.3%)	Later primary *N* = 18,993 (23.7%)	All primary *N* = 80,074
Hawaii	5,776 (1.8)	1,123 (1.8)	340 (1.8)	1,463 (1.8)
Iowa	22,532 (7.0)	4,313 (7.1)	1,355 (7.1)	5,668 (7.1)
New Mexico	9,546 (3.0)	1,591 (2.6)	376 (2.0)	1,967 (2.5)
Seattle	19,413 (6.1)	3,936 (6.4)	1,368 (7.2)	5,304 (6.6)
Utah	9,949 (3.1)	1,653 (2.7)	443 (2.3)	2,096 (2.6)
Atlanta	10,493 (3.3)	2,000 (3.3)	598 (3.1)	2,598 (3.2)
San Jose	9,260 (2.9)	1,721 (2.8)	469 (2.5)	2,190 (2.7)
Los Angeles	30,262 (9.4)	5,611 (9.2)	1,628 (8.6)	7,239 (9.0)
Rural Georgia	935 (0.3)	157 (0.3)	35 (0.2)	192 (0.2)
Greater California	48,584 (15.2)	8,490 (13.9)	2,744 (14.4)	11,234 (14.0)
Kentucky	18,661 (5.8)	3,256 (5.3)	992 (5.2)	4,248 (5.3)
Louisiana	15,862 (5.0)	3,200 (5.2)	993 (5.3)	4,193 (5.2)
New Jersey	36,189 (11.3)	7,140 (11.7)	2,440 (12.8)	9,580 (12.0)
Greater Georgia	20,040 (6.3)	3,520 (5.8)	1,015 (5.3)	4,535 (5.7)
Medicare coverage (months)[c], median (IQR)				
Part A, B, non-HMO	67 (42–82)	71 (42–84)	74 (48–85)	72 (43–84)
Part D	18 (0–52)	17 (0–48)	15 (0–49)	16 (0–49)
Number of physician visits per 6 months[d], median (IQR)	3.0 (1.3–5.5)	3.1 (1.4–5.8)	4.3 (2.3–7.1)	3.4 (1.5–6.1)
Any low-income subsidy/Medicaid eligibility[e], *n* (%)				
Ever	37,034 (11.6)	6695 (11.0)	1,720 (9.1)	8,415 (10.5)
Never	130,922 (40.9)	24,398 (39.9)	9,176 (48.3)	33,574 (41.9)
Unknown	152,340 (47.6)	29,988 (49.1)	8,097 (42.6)	38,085 (47.6)
Comorbidity[f], *n* (%)				
Overweight/Obesity diagnoses	17,980 (5.6)	4,113 (6.7)	1,398 (7.4)	5,511 (6.9)
Smoking behavior-related diagnoses[g]	23,803 (7.4)	5,787 (9.5)	2,472 (13.0)	8,259 (10.3)
COPD	59,294 (18.5)	12,734 (20.8)	4,705 (24.8)	17,439 (21.8)
Alcohol-related diagnoses[h]	14,294 (4.5)	4,102 (6.7)	1,475 (7.8)	5,577 (7.0)
Acute/Chronic pancreatitis	3,609 (1.1)	1,685 (2.8)	591 (3.1)	2,276 (2.8)
Type 2 diabetes	90,232 (28.2)	21,993 (36.0)	7,149 (37.6)	29,142 (36.4)

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Abbreviations: COPD, chronic obstructive pulmonary disease; HMO, health maintenance organization; IQR, interquartile range; SEER, Surveillance, Epidemiology, and End Results.

[a]Controls were frequency-matched to cases by age (66–69, 70–74, 75–79, 80–84, 85–89, 90–94, and 95–99), sex, and calendar year of diagnosis (±1 year).

[b]Calendar year of cancer diagnosis or control selection.

[c]Months of Medicare coverage from entry to 12 months immediately before cancer diagnosis or control selection.

[d]Physician visit claims in the 12-month period immediately before cancer diagnosis or control selection were excluded. We also excluded claims from specialists with limited direct patient care responsibilities (i.e., radiologists, anesthesiologists and pathologists) to account for surveillance bias.

[e]Any low-income subsidy or Medicaid coverage before cancer diagnosis or control selection.

[f]Defined as one inpatient claim or two physician/outpatient claims 30 days apart, excluding the 12-month period prior to cancer diagnosis or control selection.

[g]Defined as any diagnosis of personal history of tobacco use or non-dependent tobacco use disorder.

[h]Defined as any diagnosis of alcohol-induced liver disorders, alcohol-induced psych/neurologic disorders, alcohol intoxication, non-dependent alcohol abuse, or personal history of alcoholism.

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Table 2.

Associations between autoimmune conditions and pancreatic cancers in the SEER-Medicare database, 1992–2015[a]

Autoimmune conditions	Control	First primary cases		Later primary cases		All primary cases			
	N = 320,296	*N* = 61,081	OR (95% CI)[b]	*N* = 18,993	OR (95% CI)[b]	*N* = 80,074	OR (95% CI)[b]	*P* value	P_{FDR} value [c]
Addison's disease	629	114	0.88 (0.71–1.08)	56	1.04 (0.76–1.43)	170	0.93 (0.78–1.11)	0.41	0.73
Alopecia areata	261	41	0.81 (0.57–1.14)	23	1.09 (0.67–1.78)	64	0.89 (0.68–1.18)	0.42	0.73
Amyotrophic lateral sclerosis	54	>11	1.12 (0.59–2.13)	<11	0.97 (0.31–3.03)	17	1.09 (0.62–1.91)	0.76	0.91
Ankylosing spondylitis	260	71	**1.51 (1.14–2.00)**	28	1.26 (0.80–1.98)	99	**1.45 (1.14–1.84)**	**0.002**	**0.019**
Aplastic anemia	190	34	0.77 (0.53–1.12)	24	**2.09 (1.21–3.61)**	58	1.03 (0.76–1.39)	0.84	0.91
Autoimmune hemolytic anemia	136	23	0.87 (0.55–1.39)	13	1.11 (0.57–2.14)	36	0.96 (0.66–1.40)	0.82	0.91
Autoimmune hepatitis	34	<11	0.97 (0.42–2.27)	<11	0.86 (0.15–4.97)	<11	0.95 (0.44–2.04)	0.90	0.93
Celiac disease	341	66	0.95 (0.72–1.25)	24	1.05 (0.66–1.68)	90	0.97 (0.76–1.23)	0.79	0.91
Chronic rheumatic heart disease	6,073	1,328	1.03 (0.96–1.09)	483	0.93 (0.83–1.03)	1,811	1.00 (0.95–1.06)	0.96	0.96
Crohn's disease	961	212	1.11 (0.95–1.30)	83	1.11 (0.86–1.44)	295	1.11 (0.97–1.27)	0.11	0.34
Dermatitis herpetiformis	81	<11	0.61 (0.31–1.20)	<11	0.92 (0.38–2.20)	17	0.72 (0.42–1.23)	0.23	0.62
Discoid lupus erythematosus	298	80	1.33 (1.03–1.72)	23	1.19 (0.72–1.96)	103	1.30 (1.03–1.64)	0.02	0.12
Erythema nodosum	47	<11	0.79 (0.35–1.81)	<11	0.76 (0.21–2.78)	<11	0.79 (0.40–1.59)	0.52	0.83
Granulomatosis with polyangiitis	69	>11	1.28 (0.73–2.25)	<11	1.30 (0.49–3.47)	22	1.28 (0.79–2.09)	0.32	0.70
Graves' disease	1,010	235	1.16 (1.00–1.35)	85	1.23 (0.95–1.59)	320	**1.18 (1.03–1.34)**	**0.01**	**0.074**
Guillain-Barré syndrome	187	>40	1.25 (0.89–1.74)	<11	0.58 (0.28–1.20)	57	1.06 (0.78–1.44)	0.69	0.89
Hashimoto's thyroiditis	1,116	214	1.00 (0.86–1.17)	97	1.11 (0.88–1.41)	311	1.03 (0.91–1.18)	0.60	0.86
Hypersensitivity angiitis	92	>11	0.92 (0.53–1.58)	<11	0.81 (0.32–2.06)	23	0.89 (0.55–1.42)	0.62	0.86
Immune thrombocytopenic purpura	223	44	1.01 (0.72–1.42)	27	1.45 (0.91–2.32)	71	1.15 (0.87–1.51)	0.33	0.70
Localized scleroderma	522	120	1.22 (0.99–1.50)	46	1.43 (1.00–2.04)	166	**1.27 (1.06–1.52)**	**0.009**	**0.058**
Membranous nephropathy	109	>20	0.93 (0.57–1.50)	<11	0.95 (0.38–2.35)	28	0.92 (0.60–1.40)	0.68	0.89
Multiple sclerosis	502	83	0.80 (0.63–1.01)	31	0.91 (0.60–1.37)	114	0.83 (0.67–1.01)	0.07	0.26
Myasthenia gravis	370	58	0.79 (0.59–1.05)	25	0.92 (0.59–1.45)	83	0.82 (0.64–1.04)	0.10	0.34
Pernicious anemia	6,112	1,288	1.05 (0.99–1.12)	512	**1.16 (1.04–1.29)**	1,800	**1.08 (1.02–1.14)**	**0.006**	**0.045**
Polyarteritis nodosa	47	<11	0.99 (0.47–2.07)	<11	1.18 (0.40–3.50)	14	1.06 (0.58–1.95)	0.85	0.89
Polymyalgia rheumatica	3,391	727	1.11 (1.02–1.21)	231	0.97 (0.83–1.13)	958	1.07 (1.00–1.16)	0.06	0.25
Polymyositis/dermatomyositis	248	47	0.97 (0.70–1.35)	16	0.85 (0.48–1.49)	63	0.94 (0.71–1.24)	0.66	0.91

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Autoimmune conditions	Control	First primary cases		Later primary cases		All primary cases			
	N = 320,296	*N* = 61,081	OR (95% CI)[b]	*N* = 18,993	OR (95% CI)[b]	*N* = 80,074	OR (95% CI)[b]	*P* value	P_{FDR} value [c]
Primary biliary cirrhosis	160	>20	0.89 (0.59–1.35)	<11	0.64 (0.29–1.42)	37	0.82 (0.57–1.19)	0.30	0.70
Primary sclerosing cholangitis	602	206	**1.42 (1.19–1.69)**	76	1.28 (0.96–1.70)	282	**1.37 (1.18–1.59)**	**3.7×10^{-5}**	**5.6×10^{-4}**
Psoriasis	4,079	834	1.05 (0.97–1.14)	312	1.05 (0.92–1.19)	1,146	1.06 (0.99–1.13)	0.12	0.34
Pure red cell aplasia	1,074	172	0.85 (0.72–1.01)	235	**2.00 (1.68–2.37)**	407	**1.31 (1.16–1.47)**	**8.4×10^{-6}**	**1.9×10^{-4}**
Reactive arthritis	27	<11	0.89 (0.33–2.38)	<11	0.43 (0.05–3.65)	<11	0.76 (0.31–1.85)	0.54	0.84
Rheumatic fever	137	>30	1.31 (0.89–1.95)	<11	0.78 (0.33–1.82)	41	1.16 (0.82–1.66)	0.40	0.73
Rheumatoid arthritis	11,182	2,318	1.02 (0.97–1.07)	716	**0.89 (0.81–0.97)**	3,034	0.98 (0.94–1.02)	0.39	0.73
Sarcoidosis	390	96	1.18 (0.93–1.50)	25	0.67 (0.43–1.05)	121	1.03 (0.84–1.27)	0.78	0.91
Scleritis	346	73	1.20 (0.92–1.57)	17	0.72 (0.42–1.22)	90	1.07 (0.84–1.36)	0.57	0.86
Sjögren's syndrome	872	172	1.06 (0.89–1.26)	64	1.04 (0.78–1.39)	236	1.06 (0.91–1.22)	0.46	0.77
Systemic lupus erythematosus	963	214	1.13 (0.97–1.32)	71	0.95 (0.72–1.25)	285	1.08 (0.94–1.23)	0.28	0.69
Systemic sclerosis	285	43	0.76 (0.54–1.05)	17	0.97 (0.55–1.70)	60	0.80 (0.60–1.06)	0.12	0.34
Takayasu's arteritis	17	<11	0.61 (0.13–2.79)	<11	0.48 (0.05–4.84)	<11	0.57 (0.16–2.01)	0.38	0.73
Temporal arteritis	912	205	1.15 (0.98–1.35)	68	1.11 (0.84–1.48)	273	1.14 (0.99–1.30)	0.07	0.26
Type 1 diabetes	15,932	4,378	**1.13 (1.08–1.17)**	1,402	1.06 (0.99–1.13)	5,780	**1.11 (1.07–1.15)**	**5.1×10^{-9}**	**2.3×10^{-7}**
Ulcerative colitis	1,585	347	1.14 (1.01–1.29)	164	1.25 (1.04–1.51)	511	**1.18 (1.07–1.31)**	**0.001**	**0.016**
Uveitis	558	105	0.94 (0.76–1.17)	47	1.27 (0.90–1.79)	152	1.02 (0.85–1.23)	0.81	0.91
Vitiligo	219	38	0.88 (0.62–1.26)	17	1.40 (0.78–2.50)	55	0.98 (0.73–1.33)	0.91	0.93

Abbreviations: CI, confidence interval; FDR, false discovery rate; GI, gastrointestinal; HMO, health maintenance organization; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results.

[a] Cells with < 11 observations and any cell that could be used to derive the value of a cell with < 11 observations were suppressed to comply with SEER-Medicare data use agreement.

[b] Multivariable-adjusted unconditional logistic regression models were used to calculate OR and 95% CI, adjusting for age (grouped as 66–69, 70–74, 75–79, 80–84, 85–89, 90–99 years), sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Asian, Hispanic, other/unknown), calendar year of diagnosis/selection (1992–2000, 2001–2005, 2006–2009, 2010–2015), geographic region (SEER registry), Medicaid eligibility (ever, never), average number of physician visits per 6 months in the 5 years before diagnosis/selection (quintiles), average duration of Medicare part A, B, non-HMO coverage (quintiles), Medicare low-income subsidy (ever, never, unknown), overweight/obesity (ever, never diagnosed), smoking behavior-related diagnoses (ever, never diagnosed), chronic obstructive pulmonary disease (ever, never diagnosed), alcohol-related diagnoses (ever, never diagnosed), type 2 diabetes mellitus (ever, never diagnosed), acute/chronic pancreatitis (ever, never diagnosed).

[c] P_{FDR} value was calculated based on Benjamini-Hochberg procedure using an FDR threshold of 0.10. Associations that passed Benjamini-Hochberg correction (FDR = 0.10) were considered statistically significant and shown in bold.

Int J Cancer. Author manuscript; available in PMC 2024 July 20.

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Table 3.

Associations between select autoimmune conditions and all primary pancreatic cancers by histological subtypes in the SEER-Medicare database, 1992–2015[a]

Autoimmune conditions	Control	Pancreatic ductal adenocarcinoma[b]			Pancreatic neuroendocrine tumors[c]		
	N = 320,296	*N* = 76,321	OR[d] (95% CI)	*P* value	*N* = 2,102	OR (95% CI)	*P* value
Ankylosing spondylitis	260	92	**1.42 (1.12–1.81)**	**0.004**	<11	1.88 (0.70–5.08)	0.21
Graves' disease	1,010	307	**1.18 (1.04–1.35)**	**0.01**	<11	1.25 (0.65–2.43)	0.50
Localized scleroderma	522	155	**1.24 (1.03–1.48)**	**0.02**	<11	1.90 (0.85–4.28)	0.12
Pernicious anemia	6,112	1,724	**1.08 (1.02–1.14)**	**0.008**	45	1.19 (0.89–1.61)	0.25
Primary sclerosing cholangitis	602	271	**1.38 (1.19–1.60)**	**2.8×10^{-5}**	<11	0.87 (0.36–2.13)	0.77
Pure red cell aplasia	1,074	396	**1.33 (1.18–1.49)**	**2.9×10^{-6}**	<11	0.69 (0.29–1.67)	0.41
Type 1 diabetes	15,932	5,529	**1.11 (1.07–1.15)**	**2.2×10^{-9}**	146	1.02 (0.85–1.23)	0.79
Ulcerative colitis	1,585	477	**1.16 (1.05–1.29)**	**0.005**	23	**1.78 (1.17–2.70)**	**0.007**

Abbreviation: CI, confidence interval; FDR, false discovery rate; HMO, health maintenance organization; ICD-O, International Classification of Diseases for Oncology; IPMN, intraductal papillary mucinous neoplasm; NOS, not otherwise specified; OR, odds ratio; PDAC, pancreatic ductal adenocarcinoma; PNETs, pancreatic neuroendocrine tumors; SEER, Surveillance, Epidemiology, and End Results.

[a] Autoimmune conditions showing the strongest associations with all primary pancreatic cancer cases by the univariate model in Table 2 (P_{FDR} value < 0.10) were presented in this table. Results for pancreatic cancer subtypes other than PDAC or PNETs were not shown due to very small sample size. Cells with < 11 observations and any cell that could be used to derive the value of a cell with < 11 observations were suppressed to comply with SEER-Medicare data use agreement.

[b] PDAC group was comprised of the following histological subtypes (ICD-O morphology codes): ductal adenocarcinoma, NOS (8140); ductal adenocarcinoma, excluding cystic/mucinous (8255, 8490, 8500, 8507, 8510, 8514, 8521, 8523, 8560, 8570); ductal, poorly specified (8000, 8010); ductal, specified as arising from an IPMN (8144, 8450, 8453, 8471, 8503); ductal, specified as cystic adenocarcinoma (8440, 8470, 8504); ductal, specified as mucinous adenocarcinoma (8480, 8481); other specified adenocarcinoma (8145, 8460).

[c] PNETs group consisted of the following histological subtypes (ICD-O morphology codes): endocrine, carcinoid (8240, 8243, 8244, 8245); endocrine, non-secretory (8150, 8246); endocrine, secretory (8151, 8152, 8153, 8155).

[d] Multivariable-adjusted unconditional logistic regression models were used to calculate OR and 95% CI, adjusting for age (grouped as 66–69, 70–74, 75–79, 80–84, 85–89, 90–99 years), sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Asian, Hispanic, other/unknown), calendar year of diagnosis/selection (1992–2000, 2001–2005, 2006–2009, 2010–2015), geographic region (SEER registry), Medicaid eligibility (ever, never), average number of physician visits per 6 months in the 5 years before diagnosis/selection (quintiles), average duration of Medicare part A, B, non-HMO coverage (quintiles), Medicare low-income subsidy (ever, never, unknown), overweight/obesity (ever, never diagnosed), smoking behavior-related diagnoses (ever, never diagnosed), chronic obstructive pulmonary disease (ever, never diagnosed), alcohol-related diagnoses (ever, never diagnosed), type 2 diabetes mellitus (ever, never diagnosed), acute/chronic pancreatitis (ever, never diagnosed).

NOTE: Associations that passed Benjamini-Hochberg correction (FDR = 0.10) were considered statistically significant and shown in bold.

Int J Cancer. Author manuscript; available in PMC 2024 July 20.