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# Metformin use among type 2 diabetics and risk of pancreatic cancer in a clinic-based case-control study

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## Abstract

A better understanding of the association between diabetes and pancreatic cancer (PC) may inform prevention and/or early detection strategies. Metformin has been associated with reduced risk of certain cancers, including PC, in some observational clinical studies. We assessed whether metformin use was associated with PC risk among those with type 2 diabetes (DM2), and whether metformin use modulated the association between DM2 and risk of PC. In total, 536 PC cases and 869 frequency-matched controls were recruited predominantly from University of California San Francisco medical clinics from 2006–2011. Eligible participants completed direct interviews using a structured risk factor questionnaire. The association between metformin use and PC risk was assessed using propensity score weighted unconditional logistic regression methods in analyses restricted to diabetics and adjusted multivariable logistic models in the total study population. Ever use of metformin was not associated with PC risk in analyses restricted to DM2 (N=170) participants (adjusted OR: 1.01, 95%CI: 0.61–1.68). In the total study population (N=1405) using non-diabetics as the referent group, PC risk was inversely associated with diabetes duration ($p_{trend}$<0.001). Further, when DM2 participants were grouped by ever/never use of metformin and compared with non-diabetics, metformin use did not affect the association between DM2 and PC risk (never users: OR: 1.44, 95%CI: 0.78–2.67; ever users: OR: 1.19, 95%CI: 0.72–1.99). Results from our clinic-based case-control study suggest that metformin use is not associated with PC risk among those with DM2 and does not alter the association between DM2 and PC risk.

### Keywords

pancreatic adenocarcinoma; metformin; type 2 diabetes; cancer risk

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## Introduction

Pancreatic cancer (PC) is diagnosed in approximately 45,000 U.S. adults each year, making it the ninth most common cancer in women and the tenth most common in men.[1] However, given its dismal prognosis, PC is the fourth most common cause of cancer-related mortality in both sexes, with the lowest 5-year survival rate of all major cancers at 6%.[2] With active follow up of patients this rate drops to 2%.[3] This poor prognosis is partly attributable to metastatic disease at diagnosis. Even though genomic evidence suggests that PC cells take at least 5 years to develop metastatic capability,[4] more than 80% of patients have advanced and/or metastatic disease at the time of disease presentation,[5] at which point potentially curative surgery is not an option. To date, no population-wide screening tool reduces mortality associated with this disease. Identifying risk factors and protective factors may help in the development of screening programs targeted toward individuals at particularly high risk, inform appropriate recommendations regarding modifiable lifestyle habits, and aid in PC prevention strategies.

Pancreatic cancer is more common in men than women, among blacks/African Americans compared with whites, and increases with age.[2] Established factors that increase risk include family history and inherited cancer syndromes,[6] cigarette smoking,[7] hereditary and chronic pancreatitis,[8,9] obesity,[10,11] and diabetes.[12] The association between diabetes and the development of PC is well established, although the relationship is multifaceted as diabetes is both a risk factor for PC and a potential clinical consequence of the disease.[13] Metformin, an oral biguanide medication used to treat type 2 diabetes, has demonstrated anti-neoplastic properties in several preclinical studies.[14,15] Metformin may mitigate the PC risk associated with diabetes via its hypoglycemic and hypoinsulinemic effects. Hyperinsulinemia leads to downregulation of insulin-like growth factor binding protein (IGFBP), increasing free insulin-like growth factor 1 (IGF-1).[16,17] IGF-1, which normally integrates growth hormone signals, is overexpressed in PC and enhances growth in PC cell lines.[18] By decreasing blood insulin levels, metformin may decrease free IGF-1.[14] Tumor suppressive effects also may be attributed to inhibition of the mammalian target of rapamycin (mTOR),[19] a signaling molecule that regulates cell growth and cell cycling via integration of various mitogenic signaling pathways. Furthermore, metformin induces apoptosis in PC cells via caspase activation and inhibition of the tumorigenic epidermal growth factor receptor (EGFR/MAPK) pathway.[20] Given its various mechanisms of action, the role of metformin as a potential cancer protective agent has been evaluated in multiple epidemiologic studies, and has been found to be associated with decreased risk of development of breast, colorectal, liver, and lung cancers.[21–23]

Results from studies that evaluated the association between metformin and PC risk have been inconsistent, with reduced risk in some[24–26] and no effect in others.[27–31] A summary evaluation of these studies is complicated by differences in study design and methodology, including use of different comparison arms, adjustment for different confounders, and confounding by indication in analyses of populations that included participants with and without diabetes. A recent meta-analysis of nine studies showed a reduction in PC risk with metformin use, although there was significant study heterogeneity.[21] When stratified by study design, analyses indicated a null effect of metformin vs. no metformin use, with an

inverse association observed only when metformin was compared with insulin or sulfonylurea use. No prospective randomized studies have been conducted to address this association, although two randomized controlled trials of diabetes therapy[32] were secondarily analyzed to assess the effect of metformin on cancer risk. However, the low incidence of PC in these studies (20 cases over ~39,000 person years) resulted in an imprecise estimate that was not different from null.[21] In the present study, we analyzed data collected from a large clinic-based case-control study to further clarify the relationship between metformin use, diabetes, and PC risk.

## Materials and Methods

### Study Population

A case-control study of PC conducted at the University of California, San Francisco (UCSF) included patients diagnosed with exocrine adenocarcinoma of the pancreas from 2006–2011. Patients were recruited from the UCSF Gastrointestinal Medical and Surgical Oncology clinics with supplemental recruitment of patients from California Pacific Medical Center Medical and Surgical Oncology clinics as well as from the Cancer Prevention Institute of California's early case ascertainment. Eligible patients were 21–85 years old at diagnosis and able to complete a direct interview in English. Diagnoses were confirmed by patients' medical records, cancer registry and Surveillance Epidemiology and End Results abstracts that include histologic confirmation of diagnoses. Controls were recruited from the UCSF General Medicine Primary Care clinics and were frequency-matched to cases by sex and age in 5-year groups. Eligibility criteria for controls were the same as for cases with the exception of PC diagnoses. In total, 536 cases and 869 controls were eligible and completed the interview for a participation rate of 72% for eligible cases and 53% for eligible controls. All participants provided informed consent for interview and accession of medical record data pertaining to their pancreatic condition and for follow-up contact. The study was approved by UCSF's Committee on Human Research (ID: 10-00503, re-approved 10/14/2013).

### Data collection

Data were collected during direct interviews using a main risk factor questionnaire and the Block Brief 2000 food-frequency questionnaire. Participants were queried about demographic characteristics and various known or suspected PC risk factors, including recent and past weight/height, lifestyle factors such as cigarette smoking, alcohol use and diet, and personal and family medical history. Information about most exposures was restricted to a referent date of one or more years before diagnosis (cases) or interview (controls). Relevant to these analyses, participants were asked whether, more than one year before diagnosis (cases) or interview (controls), they had ever been diagnosed with diabetes by a physician, the type of diabetes, and their age at diagnosis. Cue cards with brand and generic medication names were used to help facilitate recall of medication use. Data pertaining to medications taken at least 4 days per week for at least 3 months were recorded including drug name, ages first and last used, and duration of use. In-person interviews were conducted with 67% and telephone interviews with 16% of participants, while 17% of

interviews were started in person and finished over the telephone. No proxy interviews were conducted.

## Statistical analysis

All statistical analyses were conducted using SAS software v9.3 (SAS Institute, Inc., Cary, NC). Preliminary analyses of the association between discrete or continuous factors of interest and disease status were conducted using parametric and non-parametric statistics including t-test and Wilcoxon rank-sum test. Continuous factors also were evaluated as categorical variables based on established groups or quantiles of the distribution among controls and similarly assessed using a $\chi^2$ test. Collinearity between potential confounding variables was examined using Spearman rank-order correlation. Age at PC diagnosis (cases) or interview (controls) was grouped as ≤50, 51–60, 61–70, >70 years old. Body mass index (BMI) was computed as usual adult weight/height$^2$ (kg/m$^2$) and grouped per World Health Organization categories as normal/underweight (BMI <25), overweight (BMI: 25–30) and obese (BMI >30). Alcohol consumption was analyzed as average drinks/week over the past 10 years and cigarette smoking status as never smoker, quit>15y ago, quit 1–15y ago, quit <1y ago/current smoker. Ethnicity was analyzed as a dichotomous variable: non-Hispanic white and all other ethnic groups.

Here we address the hypotheses that 1) in the population of patients with type 2 diabetes, those who use metformin are less likely to develop PC; and 2) the risk for PC associated with diabetes is attenuated among patients who use metformin. Thus, analyses of diabetes were restricted to patients who reported diagnosis of type 2 diabetes (N=170); 11 patients with type 1 diabetes were excluded from these analyses. Duration of diabetes was grouped in 5-year increments based on disease biology and data from the published literature, which also ensured adequate group sample size for analyses. The association between PC risk and specific classes of diabetes medications were assessed in non-mutually exclusive groups based on never-ever use. Unconditional logistic regression models, adjusted for matching factors and other diabetes medication use, were used to compute odds ratios (OR) with 95% confidence intervals as estimates of relative risk. Mediation of the association of BMI and PC through diabetes was assessed in stratified and conditional analyses.[33]

Because of the restricted sample size and to increase causal inference, the relationship between metformin use and PC risk in the subgroup of patients with diabetes was evaluated using propensity score methods to adjust for potential confounders. Propensity score model fit was assessed using area under a receiver operating curve for metformin never/ever use and Akaike Information Criteria for analyses of metformin duration. Adequate performance of the propensity score model was assessed by examining whether each covariate used to model the score was balanced between metformin exposure groups. Analysis of never/ever use was limited to the 161 diabetes patients (77 cases, 84 controls) who fit exchangeability criteria i.e. patients who used metformin could be “exchanged” with non-users based on their covariate profile. The propensity score for never-ever use of metformin included age, sex, race, BMI, history of pancreatitis, alcohol, smoking, family history of PC, and other diabetes drugs. Duration of metformin use was independently analyzed as a continuous variable and as quartiles of duration. A separate propensity score was estimated for the

ordinal duration variable, utilizing all 170 diabetic participants. The propensity score for duration of metformin use modeled the same factors as for metformin never-ever. Finally, unconditional logistic regression models, weighted by the inverse probability of each participant being in a given exposure group based on propensity score[34–36] were used to estimate adjusted ORs for level of metformin duration. To test the broader question of the effect of metformin use on diabetes-associated PC risk, standard multivariable unconditional logistical regression techniques were used. Non-diabetics were used as the referent group and models were adjusted for the same factors included in the propensity score. Linear trend in odds ratios was determined based on the Wald chi-square statistic for the factor when included as an ordinal variable in multivariable unconditional logistic models. Effect modification by sex was explored in stratified analyses. Stratification did not materially change point estimates but weakened precision, thus combined analyses are presented.

Raw data are not tabled for analyses with fewer than 5 participants in a cell. All models were adjusted for matching factors, age and sex. All statistical tests were two-sided and considered statistically significant when $p<0.05$.

## Results

In total, 1405 participants (536 cases and 869 controls) completed interviews and were included in these analyses (Table 1). Men constituted 53.0% of cases and 48.3% of controls. Cases were slightly older, with a median age of 63 years vs 60 years for controls. Most participants (85.2%) were non-Hispanic white, and roughly half (50.2% cases, 45.7% controls) were overweight or obese. Frequencies of cigarette smoking were identical, with 51.1% of cases and controls ever having smoked. Cases were more likely to have consumed alcohol, have pancreatitis, or have a family member with PC. Type 2 diabetes also was more prevalent in cases (15.1% vs 10.2%), a discrepancy driven by markedly different rates of recently diagnosed diabetes (7.3% vs 2.7%).

### Type 2 diabetics

A majority of type 2 diabetics reported ever having used metformin (66.5%), whereas ever use of secretagogues (38.2%), insulin (27.6%), or thiazolidinediones (17.6%) was less common (Table 2). Among type 2 diabetics (N=170), results from models conditionally adjusted for each type of diabetes medication showed that PC risk was not associated with ever use of metformin or any other specific type of diabetes medication (Table 2). When the association between PC risk and metformin use was assessed in the propensity score adjusted model, the OR for metformin use was closer to the null (OR: 1.01, Table 3). Increased total duration of metformin use (in quartiles) was inversely associated with PC risk in minimally adjusted models ($p_{trend}=0.02$, Table 3), although individual ORs were imprecise and not statistically significant. In the propensity score adjusted model, this decreased linear trend in PC risk with increased metformin duration was no longer statistically significant ($p_{trend}=0.20$, Table 3). Preliminary analyses showed a strong correlation between duration of diabetes and duration of metformin use among type 2 diabetics (Spearman rho=0.74, $p<0.0001$); therefore, the confounding due to diabetes duration was evaluated. Including diabetes duration in the propensity score adjusted model

substantially modified the association between duration of metformin use and PC risk ($p_{trend}$=0.52), particularly for OR estimates for the longest duration of use. All effects remained statistically nonsignificant. Stratification by sex revealed no statistically significant differences, although small sample sizes limited the analysis.

### Type 2 diabetics and non-diabetics

Type 2 diabetes was associated with a 40% increased risk of PC that was attenuated and no longer statistically significant in fully adjusted models (OR: 1.28, 95%CI: 0.81–2.00, Table 4). Increased duration of diabetes was inversely associated with PC risk, with statistically significant elevated ORs limited to those with diabetes of short disease duration (1–5 years versus no diabetes OR: 2.47, 95%CI: 1.25–4.85). In fully adjusted models, the increased risk of PC among those with diabetes of short duration (1–5 years) was modestly attenuated (Table 4) whereas those with longstanding diabetes (10 years or longer) were less likely to be diagnosed with PC (OR: 0.44, 95%CI: 0.18–1.08). Metformin use did not confound the association of diabetes with PC; ORs did not differ for diabetics who never and ever had used metformin (p=0.57, Table 5a). Stratification by sex revealed no significant variation in PC risk. Analyses of diabetes duration stratified by duration of metformin use were constrained by small numbers in some cells, but again showed increased risk of PC limited to those with diabetes of short duration (Table 5b). Few exposed participants precluded our ability to robustly assess whether duration of metformin use altered the association between longstanding diabetes and PC risk (Table 5b).

## Discussion

This case-control study addresses two unresolved areas of research: the association between metformin use and PC risk among type 2 diabetics, and the effect of metformin use on diabetes-associated PC risk compared to a non-diabetic population. Our data do not support a relationship between metformin and PC risk within either study context. Specifically, we did not identify any association between ever use of metformin and change in PC risk among type 2 diabetics. In a minimally adjusted model, duration of metformin exposure was statistically significantly and inversely associated with PC risk. However, propensity score weighting for significant confounders eliminated this relationship. Moreover, stratification of diabetics by never-ever metformin use or duration of metformin exposure revealed no statistically significant association between metformin and diabetes-related PC risk, although small sample size in some categories precluded robust conclusions.

Previous case-control studies that investigated the association between metformin use and PC risk have focused on slightly different research hypotheses. In a U.S. study, Li and colleagues investigated the association between metformin use and PC risk and focused their analyses on the subgroup of diabetics in their study population. These investigators demonstrated a reduced risk of PC among those who had ever used metformin (OR: 0.38 95%CI: 0.22–0.69), noting an exceptionally low risk (OR: 0.18 95%CI: 0.09–0.38) among those who reported use of metformin for >5 years.[26] In contrast, Bodmer *et al* conducted a similar analysis, but inclusive of non-diabetics, within the UK-based General Practice Research Database, and found that long-term metformin use (≥30 prescriptions) was not

associated with PC risk (OR: 0.87 95%CI: 0.59–1.29).[29] However, suggestion of an interaction by sex was reported, with a statistically significant decreased PC risk observed among women (long-term metformin use OR: 0.43 95%CI: 0.23–0.80). The disparate results between these studies may be explained by a number of factors: inclusion or exclusion of non-diabetics in the analyses; different control recruitment methods; and adjustment for different sets of confounders and for diabetes duration. As such, a direct comparison of results between these studies is challenging.

Diabetes is considered a risk factor for PC, a hypothesis supported by data from multiple cohort studies and meta-analyses.[12,37,38] However, diabetes diagnosed shortly before PC diagnosis is very unlikely to be an etiologic factor but rather a consequence of the disease,[39–41] and inclusion of these cases would bias risk estimates due to misclassification of the exposure. Further, causal inference is enhanced by maximizing the likelihood that diabetes precedes PC development. For these reasons, diabetes diagnosed within 1 year of PC diagnosis (cases) or interview (controls) was not collected in our study, where we showed an overall elevated but statistically non-significant risk of PC in participants with type 2 diabetes. Of note, previous studies have used varying diabetes duration thresholds to categorize participants as pre-diagnosis/interview diabetics,[13] and the most appropriate classification criteria remain unknown.

Confounding by indication is a concern in studies similar to ours where the effect of interest (here metformin) occurs only in the presence of a condition (diabetes) that is associated with the outcome of interest (PC). Our analysis incorporated both of the approaches used in previously published case-control studies of metformin use and PC risk. Specifically, like Li *et al*, we controlled for confounding by indication by conducting an analysis limited to diabetics, addressing the hypothesis that metformin use is associated with decreased PC risk in a diabetic population. Similar to Bodmer *et al*, we also assessed the effect within the total population of both diabetics and non-diabetics while adjusting for diabetes duration, testing a separate hypothesis that metformin use is associated with decreased PC risk relative to the general population.

As with previous observational studies,[13,42] we observed an inverse association between diabetes duration and PC risk. This effect was driven by a statistically significant increased risk in short-term (1–5 years) diabetics, raising the possibility that occult PC may have been present for multiple years at the time of diabetes diagnosis in some of the cases, even after exclusion of those with diabetes for <1 year. Under the assumption that duration of metformin use is likely to be tightly correlated with duration of diabetes, short-term metformin use might simply track with short-term (recent-onset) diabetes, and as such reflect diabetes caused by PC, in contrast to longer metformin exposure and hence longer-term diabetes. This would conceivably produce a dose-related association between metformin and PC risk that mimics that of diabetes and PC risk. Interestingly, the previous analyses by both Li and Bodmer did not formally evaluate the correlation between duration of diabetes and metformin use, and used different methods to account for this complicated relationship. Li *et al* analyzed metformin duration in the subset of diabetics with >2 years of disease but did not adjust for diabetes duration. The association between long-term metformin use and decreased PC risk was lessened but remained statistically significant

(OR: 0.18 95%CI: 0.09–0.38 in all diabetics versus OR: 0.30 95%CI: 0.13–0.69 in diabetics >2 years). Bodmer *et al*, in their analysis of those with and without diabetes, also restricted diabetes to that diagnosed >2 years before diagnosis but, unlike Li *et al*, adjusted for diabetes duration. Neither study provided estimates of linear correlation between diabetes duration and duration of metformin use. In our analysis, duration of diabetes and of metformin use were moderately correlated, and controlling for diabetes duration removed any suggestion of an association between metformin use and PC risk. The change in risk estimate was most notable among long-term users of metformin (≥ 12 years). Thus, our results could be interpreted as consistent with those either of Li or of Bodmer, depending on which modeling convention we adopted. This highlights how differences in analytic approaches can result in seemingly heterogeneous results across studies.

By broadening analyses to the entire study population, we also examined the effect modification of metformin use on the association between type 2 diabetes and risk of PC. Small sample size precluded our ability to obtain robust estimates in some analyses, but overall there was no evidence that ever use or longer use of metformin altered the association between diabetes or diabetes duration and PC risk. Stratification by sex likewise revealed no significant effect modification. This analysis has been previously conducted in only one cohort study, which similarly showed no significant association.[24] However, that analysis also was statistically limited due to few PC cases (28 total PC cases with diabetes).

Metformin has been hypothesized to decrease PC risk in part through its hypoinsulinemic effect.[14] Consistent with this theory, secretagogues and exogenous insulin, diabetes drugs that induce a hyperinsulinemic state, have been observed to increase PC risk.[25,26,29] Though use of either of these drug classes trended towards increased PC risk in preliminary analyses, relatively few diabetic patients in our study population used these medications, limiting the statistical power of our study to assess their effects.

Strengths of this clinic-based case-control study include the large sample size and high case participation rate. In a previously conducted population-based study of PC in the San Francisco Bay Area, a significant proportion of patients died prior to study contact.[3,43,44] In the current study, recruitment of patients in the clinic helped minimize the potential for survival bias. Detailed information on potential confounding variables was gathered using validated questionnaires. Confirmation of diagnoses was obtained from medical records and cancer registry data. A rigorous statistical approach to data analysis, including elimination of confounding by indication, use of propensity scores and examination of the link between metformin duration and diabetes duration, allowed us to optimize the accuracy, precision, and causal inference of this study.

Limitations of our analysis include the absence of pharmacy records to confirm duration of medication use or medication doses, as well as the potential for recall bias inherent in case-control studies. Attempts to minimize patient misreporting included direct interviews (no proxy interviews) conducted by trained interviewers and the use of cue cards to facilitate patient recall. A prospective cohort or randomized controlled design could assuage this bias, but the rarity of PC limits the number of cancer diagnoses captured in these types of studies. Therefore, case-control data examining PC risk should be interpreted in parallel with

previously published cohort studies. Additionally, while clinic-based enrollment theoretically minimizes survival bias, the setting of this study at an academic center could potentially limit generalizability to the entire population. For example, many PC patients are referred to UCSF for surgery, salvage treatment, or potential clinical trial enrollment; these therapeutic options necessitate good functional status, and thus UCSF patients may, on average, be healthier relative to the general population of PC patients. We also note that the prevalence of smoking was lower in our cases than in a previous population-based study conducted in the same geographic area,[45] and that the representation of Caucasian patients in our analysis was disproportionately high. Finally, despite the large sample size, small numbers of patients restricted some of our detailed analyses, including careful evaluation by sex.

In conclusion, results from this San Francisco clinic-based case-control study do not support an association between metformin use and PC risk in type 2 diabetics. Similarly, use of metformin by type 2 diabetics had no significant effect on the estimated PC risk associated with diabetes relative to the non-diabetic population. Further validation of these findings is warranted in larger studies or in pooled analyses, such as through the international pancreas case-control consortium (PanC4).

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## Abbreviations

| | |
|---|---|
| **BMI** | body mass index |
| **DM2** | type 2 diabetes |
| **EGFR/MAPK** | epidermal growth factor receptor |
| **IGF-1** | insulin-like growth factor 1 |
| **IGFBP** | insulin-like growth factor binding protein |
| **mTOR** | mammalian target of rapamycin |
| **OR** | odds ratio |
| **PanC4** | pancreas case-control consortium |
| **PC** | pancreatic cancer |
| **UCSF** | University of California, San Francisco |

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## Novelty

Metformin has been hypothesized to possess anti-neoplastic properties, but whether it decreases pancreatic cancer risk remains uncertain. In this large case-control study, metformin use neither altered pancreatic cancer risk among type 2 diabetics nor modulated the diabetes/pancreatic cancer risk relationship. The authors further highlight differences in analytic techniques that may help explain inconsistencies between previously reported results. This work provides evidence against an association between metformin use and pancreatic cancer.

## Table 1

Sociodemographic characteristics for 536 pancreatic cancer (PC) cases and 869 controls in a San Francisco clinic-based case-control study of pancreatic cancer.

| | Cases (%) N=536 | Controls (%) N=869 |
|---|---|---|
| **Sex** | | |
| Male | 284 (53.0) | 420 (48.3) |
| Female | 252 (47.0) | 449 (51.7) |
| **Age** | | |
| ≤50 | 70 (13.0) | 159 (18.3) |
| 51–60 | 142 (26.5) | 299 (34.4) |
| 61–70 | 178 (33.2) | 244 (28.1) |
| >70 | 146 (27.2) | 167 (19.2) |
| **Race** | | |
| Caucasian | 453 (84.5) | 744 (85.6) |
| Non-Caucasian | 83 (15.5) | 125 (14.4) |
| **BMI** | | |
| ≤25 | 267 (49.8) | 472 (54.3) |
| 25–<30 | 205 (38.3) | 265 (30.5) |
| ≥30 | 64 (11.9) | 132 (15.2) |
| **Cigarette Smoking** | | |
| Never Smoker | 262 (48.9) | 425 (48.9) |
| Quit >15 years ago | 147 (27.4) | 248 (28.5) |
| Quit 1–15 years ago | 57 (10.6) | 91 (10.5) |
| Current Smoker | 70 (13.1) | 105 (12.1) |
| **Weekly Alcohol Use** | | |
| Non-drinker | 190 (35.4) | 347 (39.9) |
| 1–7 drinks/week | 221 (41.2) | 362 (41.7) |
| 8–14 drinks/week | 71 (13.3) | 67 (7.7) |
| 15–21 drinks/week | 29 (5.4) | 35 (4.0) |
| ≥22 drinks/week | 25 (4.7) | 58 (6.7) |
| **Pancreatitis**[1] | | |
| No | 496 (92.7) | 852 (98.0) |
| Yes | 39 (7.3) | 17 (2.0) |
| **Family History of PC** | | |
| No | 507 (94.6) | 835 (96.1) |
| Yes | 29 (5.4) | 34 (3.9) |
| **Type 2 Diabetes** | | |
| No | 455 (84.9) | 780 (89.8) |
| Yes | 81 (15.1) | 89 (10.2) |
| **Diabetes Duration** | | |
| None | 455 (84.9) | 780 (89.8) |
| 1–<5 years | 39 (7.3) | 23 (2.7) |

| | Cases (%) N=536 | Controls (%) N=869 |
|---|---|---|
| 5–<10 years | 19 (3.5) | 25 (2.9) |
| ≥10 years | 23 (4.3) | 41 (4.7) |

[1] Unknown: N=1.

## Table 2

ORs and 95%CIs for pancreatic cancer related to type-2 diabetes medication use in a San Francisco clinic-based case-control study of pancreatic cancer.

| | Cases (%) N=81 | Controls (%) N=89 | OR[1] (95% CI) |
|---|---|---|---|
| **Metformin** | | | |
| No | 28 (34.6) | 29 (32.6) | 1.00 |
| Yes | 53 (65.4) | 60 (67.4) | 0.81 (0.42–1.58) |
| **Insulin Secreteagogues** | | | |
| No | 49 (60.5) | 56 (62.9) | 1.00 |
| Yes | 32 (39.5) | 33 (37.1) | 1.12 (0.58–2.14) |
| **Thiazoladinediones** | | | |
| No | 67 (82.7) | 73 (82.0) | 1.00 |
| Yes | 14 (17.3) | 16 (18.0) | 0.80 (0.35–1.86) |
| **Insulin** | | | |
| No | 56 (69.1) | 67 (75.3) | 1.00 |
| Yes | 25 (30.9) | 22 (24.7) | 1.48 (0.74–2.99) |

[1] Adjusted for age, sex, and other classes of diabetes drugs.

**Table 3**

ORs and 95%CIs for pancreatic cancer related to metformin use and duration of use in a San Francisco clinic-based case-control study of pancreatic cancer.

| | Cases (%) N=81 | Controls (%) N=89 | Minimally Adjusted OR[1] (95%CI) | Partially Adjusted OR[2] (95%CI) | Fully Adjusted OR[3] (95%CI) |
|---|---|---|---|---|---|
| **Metformin Use** | | | | | |
| No | 28 (34.6) | 29 (32.6) | 1.00 (ref) | --- | 1.00 (ref) |
| Yes | 53 (65.4) | 60 (67.4) | 0.83 (0.43–1.60) | --- | 1.01 (0.61–1.68) |
| **Metformin Duration (mo)[4]** | | | | | |
| 3 – 35 | 18 (23.1) | 13 (14.9) | 1.44 (0.58–3.55) | 1.30 (0.54–3.15) | 1.17 (0.47–2.91) |
| 36 – 60 | 14 (18.0) | 17 (19.5) | 0.81 (0.33–2.02) | 1.29 (0.50–3.33) | 1.21 (0.46–3.19) |
| 61 – 143 | 10 (12.8) | 13 (14.9) | 0.68 (0.25–1.86) | 0.96 (0.34–2.76) | 1.45 (0.47–4.45) |
| ≥144 | 8 (10.3) | 15 (17.2) | 0.45 (0.16–1.28) | 0.57 (0.17–1.85) | 1.16 (0.31–4.40) |
| *P for trend* | | | 0.02 | 0.20 | 0.52 |

[1] Adjusted for age and sex

[2] Weighted for propensity score (PS). PS model included age, sex, race, BMI, history of pancreatitis, alcohol, smoking, family history of PC, other diabetes drugs.

[3] Weighted for PS and adjusted for diabetes duration.

[4] Duration unknown: N=5.

## Table 4

ORs and 95%CIs for pancreatic cancer related to type 2 diabetes and duration of diabetes in a San Francisco clinic-based case-control study of pancreatic cancer.

| | Cases (%) | Controls (%) | OR[1] (95%CI) | OR[2] (95%CI) |
|---|---|---|---|---|
| **Type 2 Diabetes (>1 yr)** | | | | |
| No | 455 (84.9) | 780 (89.8) | 1.00 (ref) | 1.00 (ref) |
| Yes | 81 (15.1) | 89 (10.2) | 1.41 (1.02–1.96) | 1.28 (0.81–2.00) |
| **Diabetes Duration** | | | | |
| 1 – 5 years | 39 (7.3) | 23 (2.7) | 2.75 (1.62–4.69) | 2.47 (1.25–4.85) |
| 5 – 10 years | 19 (3.5) | 25 (2.9) | 1.21 (0.65–2.23) | 0.80 (0.34–1.87) |
| >10 years | 23 (4.3) | 41 (4.7) | 0.81 (0.47–1.38) | 0.44 (0.18–1.08) |
| *P for trend* | | | <0.001 | <0.001 |

[1] Adjusted for age and sex

[2] Adjusted for age, sex, race, BMI, history of pancreatitis, alcohol, smoking, family history of PC, diabetes drugs.

**Table 5a, 5b**

ORs and 95%CIs for pancreatic cancer related to type 2 diabetes stratified by metformin exposure in a San Francisco clinic-based case-control study of pancreatic cancer

| Diabetes | Metformin Use | Cases/Controls | OR[1] (95% CI) |
|---|---|---|---|
| No | --- | 455/780 | 1.00 (ref) |
| Yes | No | 28/29 | 1.44 (0.78–2.67) |
| Yes | Yes | 53/60 | 1.19 (0.72–1.99) |

**Table 5b**

| | No Metformin N = 28/29 | | Metformin Use ≤5 years N = 32/30 | | Metformin Use >5 years N = 18/28 | |
|---|---|---|---|---|---|---|
| **Diabetes Duration** | **N** | **OR[1] (95% CI)** | **N** | **OR[1] (95% CI)** | **N** | **OR[1] (95% CI)** |
| None[2] | | 1.00 | | 1.00 | | 1.00 |
| 1–5 years | 16/12 | 2.12 (0.89–5.02) | 23/11 | 2.77 (1.26–6.09) | | -- |
| 5–10 years | 7/6 | 1.12 (0.29–4.35) | 8/13 | 0.58 (0.20–1.69) | */* | 1.06 (0.23–4.88) |
| >10 years | */* | 0.36 (0.09–1.39) | */* | 0.09 (0.01–1.26) | 14/22 | 0.84 (0.32–2.25) |

[1] Adjusted for age, sex, race, BMI, history of pancreatitis, alcohol, smoking, family history of PC, diabetes medications. ORs for diabetes with metformin use and diabetes without metformin use are not significantly different (p=0.57).

[1] Adjusted for age, sex, race, BMI, history of pancreatitis, alcohol, smoking, family history of PC, diabetes drugs.

[2] Referent group is non-diabetics (n=1235).

* Sample sizes of groups with ≤5 cases or controls are redacted to preserve anonymity.