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Anti-diabetic therapies affect risk of pancreatic cancer

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Abstract

Background & Aims—Anti-diabetic drugs have been found to have various effects on cancer in experimental systems and in epidemiological studies, although the association between these therapeutics and the risk of human pancreatic cancer has not been explored. We investigated the effect of anti-diabetic therapies on the risk of pancreatic cancer.

Methods—A hospital-based, case-control study was conducted at M.D. Anderson Cancer Center from 2004 through 2008 involving 973 patients with pancreatic adenocarcinoma (including 259 diabetics) and 863 controls (including 109 diabetics). Information on diabetes history and other risk factors was collected by personal interview. The frequencies of use of insulin, insulin secretagogues, thiazolidinediones, metformin and other antidiabetic medications among diabetics were compared between cases and controls. The risk of pancreatic cancer was estimated using unconditional logistic regression analysis.

Results—Diabetics that had taken metformin had a significantly lower risk of pancreatic cancer, compared with those that had not taken metformin (OR=0.38; 95% CI, 0.22–0.69; P=0.001) with adjustments for demographic, clinical and risk factors. This difference remained statistically significant when the analysis was restricted to patients with a duration of diabetes >2 years or those never used insulin. In contrast, diabetics that had taken insulin or insulin secretagogues had a significantly higher risk of pancreatic cancer, compared with diabetics that had not take these drugs. Use of thiazolidinediones did not significantly modify pancreatic cancer risk.

Conclusions—Metformin use was associated with reduced risk, and insulin or insulin secretagogues use were associated with increased risk of pancreatic cancer in diabetics.

Introduction

Pancreatic cancer is the fourth leading cause of death from cancer for both men and women in the United States.[1] Cigarette smoking, obesity, and family history of pancreatic cancer have

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been recognized as risk factors for pancreatic cancer.[2] The association of type II diabetes mellitus (DM2) and pancreatic cancer is complex. On one hand, DM2 can occur as a consequence of pancreatic cancer.[3,4] On the other hand, there is accumulating evidence to strongly support a significant role of DM2 in pancreatic carcinogenesis.[5,6] Insulin resistance, which is initially characterized by hyperglycemia and hyperinsulinemia, is a proposed mechanism underlying the association of DM2 or obesity with cancer.[7,8] A growth-promoting hormone with mitogenic effects, insulin could also upregulate the bioavailability of insulin-like growth factor 1(IGF1)by displacing it from binding proteins.[9] In addition, exocrine pancreatic tissue may be chronically exposed to local insulin concentrations much higher than the circulating insulin levels seen in hyperinsulinemic patients.[10]

Although the association between DM2 and several types of human cancers are well established, few studies have investigated the role of antidiabetic therapies might have on this relationship. There are therapies for DM2 that increase the circulating insulin levels, e.g. exogenous insulin or insulin analogs, insulin secretagogues (sulfonylureas and meglitinides) as well as treatments that reduce the insulin resistance, e.g. biguanides and thiazolidinediones. [11] Two recent epidemiological studies have found that diabetic patients treated with the biguanide metformin were less likely to develop cancer but that those treated with insulin or sulfonylurea were more likely to die of cancer.[12,13] However, these studies did not specify the types of cancer affected. In experimental systems, metformin has been shown to have antioxidant and tumor growth inhibition activities.[14-17] In a study using a hamster model, metformin had a significant protective effect against the development of pancreatic tumors induced by chemical carcinogens and a high fat diet.[18] However, to our knowledge, no studies have been reported on the association of antidiabetic therapies and pancreatic cancer risk in humans. We therefore examined the association of antidiabetic therapies and pancreatic cancer risk in a large hospital-based case-control study.

Materials and Methods

Study Population

The study population consisted of patients from an ongoing hospital-based case-control study conducted at The University of Texas M.D. Anderson Cancer Center that began in 2004. The purpose of the ongoing study was to define environmental and genetic factors that contribute to the development of pancreatic cancer. The study was approved by the M.D. Anderson Cancer Center Institutional Review Board. The study design and patient population has previously been described in detail.[19] Cases were consecutively recruited from patients with newly diagnosed and pathologically confirmed pancreatic ductal adenocarcinoma who were seen at the M.D. Anderson Gastrointestinal Center. Controls were recruited from healthy individuals accompanying patients being treated at other centers in our institute. The controls were mostly spouses, and others were non-blood relatives and friends of patients with cancers other than gastrointestinal or smoking-related cancers, and controls were not genetically related to the patients. Cases and controls were frequency-matched by age (± 5 years), sex, and race. All study subjects (both cases and controls) were U.S. residents, had no prior history of cancer (except non-melanoma skin cancer), and were able to communicate in English. Each study participant gave written informed consent to participate in a personal interview and to have a blood sample collected. As of May 2008, when the current analysis was conducted, a total of 1004 eligible cases and 867 controls were recruited and completed the interview. The recruitment rate (number of individuals recruited/number of individuals approached) was 81% for cases and 77% for controls. Thirty-one cases who were later not pathologically confirmed as pancreatic adenocarcinoma and 4 controls who had incomplete questionnaire data were excluded from the analysis, leaving 973 cases and 863 controls in the current study.

Data Collection

Trained personnel administered a structured and validated questionnaire[20] to collect information on demographics and known or suspected risk factors for pancreatic adenocarcinoma, e.g. cigarette smoking, alcohol consumption, family history of cancer, and medical history. The questionnaire was administered by personal interview and no proxy interview was involved. Ever smokers were defined as individuals who had smoked more than 100 cigarettes in their lifetimes. Daily alcohol consumption (grams of ethanol per day) was calculated based on the type, duration and frequency of alcoholic drinks reported. Family history of cancer was restricted to the first-degree relatives. Mean body mass index (BMI, kg/m^2) was calculated using the self-reported body weight at age 30, 40 and 50 years old and the self-reported usual height. According to the WHO standard, BMI of 18.5 to 24.9, 25 to 29.9, and >30 kg/m^2 were defined as normal body weight, overweight, and obesity, respectively.

Diabetes was defined by the self-reported medical history. Diabetes in cancer patients was also confirmed from their medical records. Diabetes-related information included age and year of diagnosis, whether used insulin and duration of use, whether used oral antidiabetics medications, name of the medication, and duration of their use.

Hemoglobin A1C (HbA1C) Measurement

To test glycemic control in the past 90 to 120 days, HbA1C was measured in 571 pancreatic cancer cases that were recruited after 2006 using potable DCA 2000 systems (Bayer HealthCare, Tarrytown, New York). Controls were not tested because of the relatively low frequency of DM2 in the group. In general, the normal range of HbA1C for healthy individuals is less than 6%.[21] According to American Diabetes Association, HbA1C values greater than 7.0% indicate poor glycemic control for patients with diabetes.[21]

Statistical Analysis

The distribution of categorical variables was compared between cases and controls by the Pearson chi-square test. The association of pancreatic cancer with risk factors, e.g. cigarette smoking, alcohol consumption, BMI, diabetes and family history of cancer was analyzed using multivariate unconditional logistic regression analysis. Age, sex, and race were included in all models.

Participants' duration of diabetes (time from diabetes diagnosis to recruitment to the study) was categorized into one of three groups: ≤2, 3 to 5, or >5 years. Duration of diabetes was also dichotomized at 2 years to distinguish cases of DM2 from cases of diabetes caused by pancreatic cancer. Our rationale for setting the cutoff at 2 years is that pancreatic cancer progressing so rapidly that it is unlikely a case of pancreatic cancer-induced diabetes would go without the cancer detection more than 2 years.

Because the number of patients who received monotherapy was small, insulin use was not considered in the oral medication classification groups. Non-insulin antidiabetic medications were categorized into four groups: 1) insulin secretagogues, e.g., sulfonylureas and meglitinides; 2) biguanides, such as metformin; 3) thiazolidinediones (TZDs); and 4) other dugs which include alpha-glucosidase inhibitors, dipeptidyl peptidase-4, amylin analogs, and glucagon-like peptide-1 analogs. Because many patients used combination therapy, the drugs or combinations changed over time, and the number of patients in each monotherapy group was small, the final analysis used the categorical variables of ever or never use of insulin, insulin secretagogues, metformin or TZDs. Duration of use for each type of therapy was categorized into one of three groups: ≤2, 3 to 5, or >5 years. The association of oral antidiabetic therapy and risk of pancreatic cancer was analyzed in multivariable logistic regression models including age, sex, race, smoking, alcohol, BMI, family history of cancer, duration of diabetes

and insulin use. To control for reversal causality due to pancreatic cancer caused diabetes, risk of pancreatic cancer was estimated after exclusion of those with duration of diabetes ≤2 years. HbA1C level (≤7% or >7%), a marker of glycemic control, was compared between ever-users and never-users of each type of antidiabetic therapy by Chi-square test. The demographic and risk factors as well as duration of diabetes and insulin use was compared between metformin ever users and never users by Chi-square test. Fisher's exact test was applied when any of the group had <5 subjects.

All statistical analyses were performed using SPSS version 15.0 (SPSS, Cary, NC) and Stata (Stata Corp, College Station, TX) software with two-sided tests, with a *P* value of <0.05 considered statistically significant.

Results

Characteristics of the Study Population

The characteristics of the study population, including risk factors for pancreatic cancer, are summarized in Table 1. No significant differences in sex and education level were observed between cases and controls, but blacks and individuals older than 70 years were under-represented in the control group compared to the case group (*P*=0.007 and *P*=0.002, respectively).

Cigarette smoking, alcohol consumption, family history of cancer among first-degree relatives, overweight or obesity was significantly associated with an increased risk of pancreatic cancer (Table 1). Diabetes was associated with a 2.37-fold increased risk for pancreatic cancer [95% confidence interval (CI), 1.87-3.06]. Diabetes was diagnosed 18 years or younger only for two individuals, suggesting the vast majority of the diabetics in the study had type II diabetes. Patients who were diagnosed with diabetes within 2 years of recruitment to the study had an Odds ratio (OR) of 4.50 (95% CI, 2.96-6.84); those with a diabetes duration of 3-5 or >5 years had an OR of 1.71 (95% CI, 1.02-2.85, P=0.04) and 1.52 (95% CI, 1.05-2.21, P=0.028), respectively.

Association of Antidiabetic Therapy and Risk of Pancreatic Cancer

The frequencies with which each of the antidiabetic therapies were used are listed in Table 2. Using non-diabetics as the referent, a nonsignificant increase in risk of pancreatic cancer was detected for insulin secretagogues users (OR, 1.78; 95% CI, 0.69-4.56) and TZD users (OR, 1.26; 95% CI, 0.45-3.52). In contrast, a significantly reduced risk of pancreatic cancer was observed for metformin users (OR, 0.38; 95% CI, 0.21-0.67, *P*=0.001). A nonsignificant reduced risk was seen among those used metformin in combination with either insulin secretagogues or TZD.

Next we performed the analysis among subjects with diabetes only. Using never-users as the referent group, ever-users of insulin and ever-users of insulin secretagogues had 4.99 and 2.52-fold increased risks for pancreatic cancer (*P*<0.001 and *P*=0.005, respectively) (Table 3). Ever-users of metformin had a 62% reduction in the risk of pancreatic cancer (OR, 0.38; 95% CI, 0.22-0.69; *P*=0.001). Ever-users of a TZD had a 55% higher risk of pancreatic cancer compared with never-users, but the difference was not statistically significant (*P*=0.213). When the analysis was restricted to individuals who never used insulin, the risk association became stronger for insulin secretagogues ever-users and weaker for metformin ever users. When individuals with duration of diabetes ≤2 years were excluded from the analysis, the association of insulin use or metformin use and risk of pancreatic cancer remained statistically significant (Table 3).

The duration of antidiabetic therapy was evaluated for insulin, insulin secretagogues and metformin use. Using never users as the referent group, short-term use (≤2 years) of insulin, insulin secretagogues or metformin was significantly associated with risk of pancreatic cancer. However, long-term use (>5 years) of metformin but not insulin or insulin secretagogues significantly modified the risk of pancreatic cancer (Table 4). After exclusion of diabetes with duration of ≤2 years, the protective effect of metformin use against pancreatic cancer remained statistically significant; and use of insulin for >5 years also showed a significant effect on increased risk of pancreatic caner (P=0.049).

Glycemic Control and Other Potential Confounders

To demonstrate whether glycemic control was a confounding factor for the association between antidiabetic therapy and risk of pancreatic cancer, we measured HbA1C level in 571 pancreatic cancer cases that were recruited after 2006. There was no significant difference in age (*P*=0.49), sex (*P*=0.62), race (*P*=0.11), smoking (*P*=0.75), history of diabetes (*P*=0.31), duration of diabetes (*P*=0.36), insulin use (*P*=0.54) and oral antidiabetic medication use (*P*=0.32) between patients with or without the HbA1C test. A slightly higher frequency of obesity (11.4% versus 6.4%) was observed between those with or without the HbA1C test (P=0.02). Among patients with self-reported diabetes, 40.1% (63/157) had HbA1C >7.0%. Notably, among those without a history of diabetes, 25.1% (104/414) had elevated levels of HbA1C (>6.0%). Ever-users of insulin had a significantly higher frequency (58%) of poor glycemic control (HbA1C > 7%) than never users (28%) *P*<0.001). No significant differences in HbA1C levels were observed between ever-users and never-users of insulin secreatagogues (*P*=0.87), metformin (*P*=0.54) or TZD (*P*=0.78).

We also examined the distribution of demographic and risk factors between ever and never users of metformin. As shown in Table 5, among all the factors analyzed, insulin use was the only factor that showed significant difference, i.e. insulin was used among 47.6% of never users versus 25.7% ever users of metformin (*P*<0.001). To examine the potential confounding effect of cigarette smoking and obesity, two established risk factors for both pancreatic cancer and diabetes, we analyzed the association of metformin use and risk of pancreatic by smoking and obesity status. The protective effect of metformin was slightly stronger in never smokers (OR, 0.37; 95% CI, 0.17-0.81) than that in ever smokers (OR, 0.44; 95%CI, 0.18-1.09), but the interaction of metformin and smoking was not significant ($P_{interaction}$=0.56, likelihood ratio test). Similarly, the protective effect of metformin was statistically significant in individuals with normal body weight (BMI< 25 kg/m^2) (OR, 0.35; 95% CI, 0.16-0.79, *P*=0.01) but was not significant in those with excess body weight (BMI >25 kg/m^2) (OR, 0.32; 95%CI, 0.02-5.36, *P*=0.42). The *P* value for interaction of metformin and BMI was 0.79.

Discussion

To our knowledge, the current case-control study is the first to demonstrate a statistically significant association between antidiabetic therapy and risk of pancreatic cancer. Our major observations are that diabetics who ever used metformin, especially those with >5 years of use, had a reduced risk of pancreatic cancer compared to never-users. In addition, there were some suggestive observations that diabetics who had used insulin or insulin secretagogues (sulfonylureas and meglitinides) had increased risk of pancreatic cancer compared to never users. These observations are consistent with findings from two previous epidemiological investigations,[12,13] and add evidence that antidiabetic therapy can affect the development of human cancer.

Metformin, a biguanide, is an oral hypoglycemic agent commonly used for the treatment of DM2. The current study demonstrated a robust protective effect of metformin against pancreatic cancer in diabetes. Although the number of patients with diabetes in this study was

relatively small, the study has more than 80% power in detecting an OR of 0.3. Other diabetes-associated factors, such as the duration of diabetes, smoking, overweight or obesity, as well as glycemic control did not have a significant confounding effect on the relationship between metformin use and risk for pancreatic cancer. Even though a higher frequency of insulin use was observed among never users of metformin compared to ever users, the protective effect of metformin remained statistically significant when the analysis was restricted to insulin never users.

Metformin reduces the level of glucose by decreasing hepatic glucose production, increasing glucose utilization and fatty acid oxidation. Like TZDs but unlike insulin and insulin secretagogues, metformin decreases the plasma insulin level.[22] Metformin also has a modest weight-reducing effect, while the other classes of agents tend to cause weight gain.[23] Based on the current understanding, the direct molecular mechanism of action of metformin involves activation of the AMP activated protein kinase (AMPK) which is a metabolite-sensing protein kinase family that is sensitive to increases in the AMP/ATP ratio.[24] AMPK activation not only regulates many metabolic enzymes but also has been shown to inhibit the mTOR pathway, which may in turn regulate cell proliferation.[25] Furthermore, AMPK has recently been found to play a role in cell polarity and cell division.[26] Therefore, in addition to amelioration of hyperglycemia and hyperinsulinemia (factors that mediate the adverse impact of DM2 on cancer), metformin has direct effects on cancer cells to block the mitogenic effects of insulin and IGF-1 at post-receptor levels by blocking the PI3K/Akt/mTOR signaling pathway and by inhibiting cell division. Indeed, cell culture experiments as well as animal model experiments have demonstrated a direct antineoplastic effect of metformin.[27-29] Thus, the protective effect of metformin against pancreatic cancer observed in our study could be explained by the combination of all the effects of this drug discussed above.

The association of insulin ever-use and increased risk of pancreatic cancer was confounded by two factors: duration of diabetes and glycemic control. Among pancreatic cancer cases, many patients started to use insulin ≤2 years prior to their cancer diagnoses, perhaps because of worsening of diabetes caused by the cancer. Thus, the association between short-term insulin use and pancreatic cancer suggest reverse causality, i.e., occult pancreatic cancer worsened diabetes within the 2 years prior to diagnosis of pancreatic cancer, causing the patients to initiate insulin therapy for glycemic control. On the other hand, we did observe a weak but significant association between long-term insulin use (>5 years) and increased risk of pancreatic cancer (OR, 2.78; 95% CI, 1.00-7.73; P=0.049). However the statistical power was limited because this observation was made in a very small number of study subjects (17 cases and 9 controls). The association between long-term insulin use and risk of pancreatic cancer needs to be further investigated in a larger study.

Insulin secretagogues as a monotherapy for DM2 showed the highest risk of pancreatic cancer in this study. However, because of the small number of insulin secretagogues ever-users among controls, this observation could be by chance alone. Among diabetic subjects, the risk of pancreatic cancer was increased in short-term users but not long-term users of insulin secretagogues compared with never users, which do not support a role of this type of treatment on cancer. Because of the previous positive findings, the association between insulin secretagogue use and risk of pancreatic cancer should be investigated further in a larger study.

Our study has several potential limitations. As in any case-control study, recall bias is a concern. However, after cross-checking the diabetes history and information on current medications given by case subjects against their medical records, we found a high level of consistency. Moreover, a previous study indicated that 3% of survey respondents inaccurately reported their own prior histories of diabetes, which was the minimum misclassification rate among several medical conditions.[30] Our study was conducted in a single tertiary-care referral hospital, so

the data may not be generalizable to the general population. However, the prevalence of diabetes among controls in our study was quite comparable to previously reported frequencies in population-based case-control studies of pancreatic cancer.[31,32] Even though our study has a large sample size, the statistical power is still limited when the analysis was restricted to diabetic subjects. Therefore, our observations need to be confirmed in large studies. Last but not least, our study design could not demonstrate whether the reduced cancer risk is due to less severe diabetes that lead to the choice of metformin or it was due to better-controlled diabetes by use of metformin. More detailed history on time and duration of each type of antidiabetic therapy use is required to address this question.

Because pancreatic cancer is a rapidly fatal but a relatively uncommon cancer, epidemiological research on this disease is challenging. Our report seeks for replication efforts from other study populations to confirm or refute a possible role of antidiabetic therapy in pancreatic cancer. If the finding that metformin is protective against pancreatic cancer is confirmed, metformin may offer a tool for the primary prevention of pancreatic cancer among people with DM2.[11]

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Abbreviations used in this paper

CI
confidence interval

DM2
type II diabetes mellitus

IGF
insulin-like growth factor

OR
odds ratio

Table 1
Participant Characteristics and Risk Factors of Pancreatic Cancer

Characteristic	No. Cases (%)	No. Control (%)	AOR (95% CI)[a]	*P* value
Age			Matching factor	0.002
≤50 years	128 (13.1)	142 (16.5)		
51 to 60 years	267 (27.4)	285 (33.0)		
61 to 70 years	381 (39.2)	290 (33.6)		
>70 years	197 (20.2)	146 (16.9)		
Race			Matching factor	0.007
White	852 (87.6)	790 (91.5)		
Hispanic	62 (6.4)	46 (5.3)		
Black	59 (6.1)	27 (3.1)		
Sex			Matching factor	0.124
Female	393 (40.3)	318 (36.8)		
Male	580 (59.7)	545 (63.2)		
Education				
≤ Bachelor's degree	771 (79.2)	694 (80.4)	1.0	
> Bachelor's degree	202 (20.8)	169 (19.6)	1.18 (0.93-1.51)	0.178
Smoking				
Never	434 (44.7)	467 (54.1)	1.0	
Ever	539 (55.3)	396 (45.9)	1.45 (1.19-1.78)	<0.001
Family history of cancer[b]				
No	341 (35.2)	412 (47.8)	1.0	
Yes	627 (64.5)	449 (52.1)	1.62 (1.34-1.97)	<0.001
Alcohol				
Non-drinker	398 (41.0)	376 (43.6)	1.0	
Drinker	575 (59.0)	487 (56.4)	1.25 (1.01-1.55)	0.043
Body mass index				
<25 kg/m^2	538 (55.4)	648 (75.1)	1.0	
25-29.9 kg/m^2	343 (35.3)	183 (21.2)	2.58 (2.08-3.23)	<0.001
≥30 kg/m^2	90 (9.3)	32 (3.7)	4.21 (2.72-6.49)	<0.001
Diabetes[c]				
No	714 (73.3)	754 (87.4)	1.0	
Yes	259 (26.7)	109 (12.6)	2.37 (1.84-3.06)	<0.001
Duration ≤2 years	131 (13.5)	29 (3.4)	4.50 (2.96-6.86)	<0.001
3-5 years	43 (4.4)	26 (3.0)	1.71 (1.02-2.85)	0.040
>5 years	85 (8.7)	53 (6.1)	1.52 (1.05-2.21)	0.028

Abbreviations: AOR, adjusted odds ratio; 95% CI, 95% confidence interval.

[a] AORs were calculated using a logistic regression model including age, sex, race, smoking, alcohol, body mass index, history of diabetes and family history of cancer.

[b] Information on family history among first degree relatives was missing for 2 cases and 1 control because of adopted family.

[c] BMI was not included in the model because of colinearity with diabetes.

Table 2

Antidiabetic Therapy and Risk of Pancreatic Cancer among All Study Subjects

Treatment Group	No. Cases (%)	No. Control (%)	AOR (95% CI)[a]	P value
Non-diabetics	714 (73.3)	754 (87.4)	1.0	
No oral medication	60 (6.2)	16 (1.9)	0.56 (0.24-1.33)	0.189
Insulin secretagogues	47 (4.8)	7 (0.8)	1.78 (0.69-4.56)	0.231
Metformin	74 (7.6)	54 (6.3)	0.38 (0.21-0.67)	0.001
TZD	23 (2.4)	6 (0.7)	1.08 (0.37-3.18)	0.883
Insulin secretagogues & metformin	23 (2.4)	10 (1.2)	0.64 (0.25-1.66)	0.357
TZD & metformin	14 (1.4)	8 (0.9)	0.39 (0.14-1.13)	0.084
Others[b]	18 (1.8)	8 (0.9)	1.26 (0.45-3.52)	0.659

Abbreviations: AOR, adjusted odds ratio; 95% CI, 95% confidence interval; TZD, thiazolidinedione.

[a] AORs were calculated using a logistic regression model including age, sex, race, smoking, alcohol, BMI, and family history of cancer, diabetes duration, and use of insulin. Non-diabetic individuals were used as the reference group.

[b] Others include 19 individuals who used combination of insulin secretagogues and TZDs with or without metformin and 7 individuals who could not correctly recall the name of their medications.

Table 3

Antidiabetic Therapy and Risk of Pancreatic Cancer among Diabetic Subjects

Type of Therapy	All Diabetics			Never users of insulin			Duration of diabetes > 2 years		
	No. Cases/ No. Controls	AOR (95% CI)[a]	P-Value	No. Cases/ No. Controls	AOR (95% CI)[a]	P-Value	No. cases/ no. controls	AOR (95% CI)[a]	P-Value
Insulin									
Never	147/88	1.0		-[b]	-		58/63	1.0	
Ever	112/21	4.99 (2.59-9.61)	<0.001				70/16	5.04 (2.38-10.7)	<0.001
Insulin secretagogues									
Never	171/84	1.0		86/69	1.0		78/57	1.0	
Ever	84/22	2.52 (1.32-4.84)	0.005	59/17	3.82 (1.78-8.20)	0.001	48/20	1.74 (0.80-3.77)	0.160
Metformin									
Never	138/32	1.0		65/24	1.0		62/24	1.0	
Ever	117/74	0.38 (0.22-0.69)	0.001	80/62	0.44 (0.22-0.87)	0.019	64/53	0.41 (0.19-0.87)	0.020
TZDs									
Never	204/87	1.0		116/68	1.0		98/62	1.0	
Ever	51/19	1.55 (0.78-3.07)	0.213	29/18	1.22 (0.56-2.63)	0.618	28/15	1.65 (0.71-3.87)	0.245

Abbreviations: AOR, adjusted odds ratio; 95% CI, 95% confidence interval; TZD, thiazolidinedione.

[a] AOR was adjusted for age, race, sex, smoking, alcohol, BMI, family history of cancer, diabetes duration and use of insulin.

[b] Not applicable

Table 4

Duration of Antidiabetic Therapy and Risk of Pancreatic Cancer

Duration of Use (years)	All Subjects			Diabetes Duration > 2 years		
	No. Cases/No. Controls	[a]OR (95% CI)	P-Value	No. Cases/No. Controls	[a]OR (95% CI)	P-Value
Insulin						
Never use	147/88	1.0		58/63	1.0	
≤2	70/4	11.3 (3.86-33.3)	<0.001	36/1	33.5 (4.26-264)	0.001
3-5	9/0	-		9/0	-	
>5	17/9	1.30 (0.52-3.23)	0.572	17/9	2.78 (1.00-7.73)	0.049
Metformin						
Never use	138/32	1.0		62/24	1.0	
≤2	63/35	0.34 (0.18-0.63)	0.001	11/14	0.26 (0.09-0.74)	0.012
3-5	23/10	0.44 (0.18-1.09)	0.076	23/10	0.89 (0.33-2.42)	0.816
>5	29/27	0.18 (0.09-0.38)	<0.001	29/27	0.30 (0.13-0.69)	0.005
Insulin Secretagogues						
Never use	171/84	1.0		78/57	1.0	
≤2	50/6	4.94 (1.90-12.8)	0.001	14/4	1.91 (0.54-6.76)	0.314
3-5	16/7	1.05 (0.40-2.77)	0.924	16/7	1.68 (0.61-4.67)	0.317
>5	16/8	0.71 (0.27-1.90)	0.498	16/8	1.01 (0.35-2.93)	0.987

[a]OR was adjusted for age, sex, race, smoking, alcohol, BMI and family history of cancer.

Table 5

Select Variables between Metformin Ever User and Never User

Variable	N (%)		P value (χ^2)
	Ever	Never	
Age (years)			0.25
≤50	16 (8.4)	16 (9.4)	
51-60	52 (27.2)	37 (21.8)	
61-70	87 (45.5)	71 (41.8)	
>70	36 (18.8)	46 (27.1)	
Sex			0.23
Female	71 (37.2)	53 (31.2)	
Male	120 (62.8)	117 (68.8)	
Race			0.84
White	151 (79.1)	136 (80.0)	
Hispanic	21 (11.0)	20 (11.8)	
Black	19 (9.9)	14 (8.2)	
Smoke			0.34
Never	87 (45.5)	86 (50.6)	
Ever	104 (54.5)	84 (49.4)	
Body Mass Index (kg/m^2)			0.89
<25	88 (46.6)	81 (48.5)	
25-29	76 (40.2)	63 (37.7)	
≥30	25 (13.2)	23 (13.8)	
Diabetes Duration (years)			0.15
≤2	74 (38.7)	84 (49.4)	
3-5	40 (20.9)	29 (17.1)	
6-10	37 (19.4)	22 (12.9)	
>10	40 (20.9)	35 (20.6)	
Insulin Use			<0.001
No	142 (74.3)	89 (52.4)	
Yes	49 (25.7)	81 (47.6)	
HbA1C (%)			0.54
≤7	40 (57.1)	57 (62.0)	

Variable	N (%)		P value (χ^2)
	Ever	Never	
>7	30 (42.9)	35 (38.0)	