



BRIEF ARTICLE

## Diabetes mellitus as a risk factor for gastrointestinal cancer among American veterans

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### Abstract

**AIM:** To assess the risk of biliary and pancreatic cancers in a large cohort of patients with type 2 diabetes mellitus (DM).

**METHODS:** Eligibility for this study included patients with type 2 DM (ICD-9 code 250.0) who were discharged from Department of Veteran Affairs hospitals between 1990 and 2000. Non-matched control patients without DM were selected from the same patient treatment files during the same period. Demographic information included age, sex and race. Secondary diagnoses included known risk factors based on their ICD-9 codes. By multivariate logistic regression, the occurrence of biliary and pancreatic cancer was compared between case subjects with DM and controls without DM.

**RESULTS:** A total of 1172496 case and control subjects were analyzed. The mean age for study and control subjects was  $65.8 \pm 11.3$  and  $64.8 \pm 12.6$  years, respectively. The frequency of pancreatic cancer in subjects with DM was increased (0.9%) in comparison to control subjects (0.3%) with an OR of 3.22 (95% CI: 3.03-3.42). The incidence of gallbladder and

extrahepatic biliary cancers was increased by twofold in diabetic patients when compared to controls. The OR and 95% CI were 2.20 (1.56-3.00) and 2.10 (1.61-2.53), respectively.

**CONCLUSION:** Our study demonstrated that patients with DM have a threefold increased risk for developing pancreatic cancer and a twofold risk for developing biliary cancer.

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**Key words:** Diabetes mellitus; Pancreatic neoplasms; Adenocarcinoma; Gallbladder neoplasms

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### INTRODUCTION

The prevalence of type 2 diabetes mellitus (DM) is rapidly growing globally and has become a major public health problem that is approaching epidemic proportions worldwide<sup>[1,2]</sup>. Even though cardiovascular complications are a major cause of morbidity and mortality in patients with diabetes, this disease has also been associated with several cancers, most notably of the liver, endometrium, kidney, and pancreas<sup>[3-5]</sup>.

To the best of our knowledge, the relationship of DM with gallbladder and extrahepatic biliary cancers has not been reported clearly in the literature. There has also been previous discussion over the role of diabetes in the development of pancreatic cancer; and there are recent studies that have suggested an elevated risk of pancreatic cancer in patients with DM<sup>[6-8]</sup>.

Although clinical conditions associated with high levels of insulin, such as acromegaly, are related to an increased risk of colon cancer, esophageal and gastric cancer, the relationship between type 2 DM and these gastrointestinal cancers has not been well established in large studies<sup>[9,10]</sup>.

It is of great significance to investigate the relationship between type 2 DM and gastrointestinal malignancies from an epidemiological standpoint, to determine preventive measures and implement screening strategies. Distinct from most previous studies that have involved either a limited sample size or a specified cancer site, we conducted a comprehensive assessment of the risk of gastrointestinal malignancies in a large cohort of patients with DM.

## MATERIALS AND METHODS

### Data collection and data sources

The Austin Automation Center has maintained the Patient Treatment File (PTF) since July 1969. The PTF documents inpatient treatment from all Veterans Health Administration (VHA) hospitals, extended care discharges and non-VHA hospital discharges at the Veterans Administration (VA) expense. The PTF contains demographic characteristics of patients and discharge diagnoses. Since 1984, a primary diagnosis and up to nine secondary diagnoses have been recorded according to ICD9-CM<sup>[11]</sup>.

### Identification of cases and controls

Cases were defined as patients who were diagnosed with type 2 DM. Cases with ICD9-CM code 250.0 were identified from the PTF from 1990 to 2000<sup>[11]</sup>. The date of a patient's first appearance in the PTF with type 2 DM was considered the date of diagnosis. Non-matched control patients without DM were selected from the same PTF during the same time period. Controls were gathered with a 3:1 ratio in proportion to cases. A method of random selection without replacement was used to ensure that no individual control subject was selected more than once.

### Calculation of comorbidity index

A comorbidity index was calculated for cases and controls. An adaptation of the Charlson Comorbidity Index as applied to administrative databases was employed<sup>[12,13]</sup>.

### Collected information and extraction of secondary diagnoses

Demographic information consisting of age, sex and ethnicity was obtained from the computerized records for cases and controls at the time of selection. Individual social security numbers were used to search the inpatient files from 1990 to 2000 for the following malignancies: gallbladder cancer (156.0), biliary cancers (156.1, 156.8 and 156.9), and pancreatic cancer (157.0, 157.1, 157.2, 157.3, 157.8 and 157.9)<sup>[11]</sup>. To ensure an appropriate temporal relationship between diabetes and these selected malignancies, cases were excluded if diabetes was not diagnosed at least 3 years prior to the diagnosis of the selected malignancy.

We searched the inpatient files for secondary diagnoses of potential risk factors for biliary and pancreatic cancer which included the following: cholelithiasis (574.0, 574.01, 574.10, 564.11, 574.20, 574.21, 574.60, 574.61, 474.70, 574.71, 574.80, 574.81, 574.90 and 574.91); choledocholithiasis (574.30, 574.31, 574.40, 574.41, 574.50 and 574.51); cholecystitis (575.0, 575.10, 575.11 and 575.12); other gallbladder diseases (575.2, 575.3, 575.4, 575.5, 575.6, 575.8, 575.9, 576.2, 576.3, 576.4, 576.8 and 576.9); sclerosing cholangitis (576.1), pancreatitis (577.0, 577.1 and 577.2); other pancreatic diseases (251.8, 251.0, 577.8, 577.9, 579.4 and 251.9); smoking or history of smoking (305.1, 989.84, E869.4 and V15.82); obesity (278.00 and 278.01); and hypercholesterolemia (272.0)<sup>[11]</sup>.

### Statistical analysis

Statistical analysis was performed using SAS/STAT Software (SAS Institute, Cary, NC, USA)<sup>[14]</sup>.  $P < 0.05$  was interpreted as being indicative of statistical significance. Continuous variables were analyzed by unpaired  $t$  tests. Binary variables were analyzed using the  $\chi^2$  and Fisher's exact tests. Quantitative variables were expressed as means  $\pm$  SD. In the multivariable analysis, a logistic regression model was used to assess the occurrence of gallbladder, biliary and pancreatic cancers using age, ethnicity, and potential risk factors as predictor variables, while controlling for differences in comorbid conditions. OR and 95% CI were used to indicate the strength of influence.

## RESULTS

We evaluated 278 761 patients with DM and 836 283 control patients hospitalized between 1990 and 2000. Case and control groups were well matched according to their demographic information. The mean age for case and control subjects was  $65.8 \pm 11.3$  and  $64.8 \pm 12.6$  years, respectively ( $P = \text{NS}$ ). There was a preponderance of male subjects in case and control groups (97.8% and 97.4%, respectively). Also, in the DM group, 66.3% were Caucasian compared to 68.3% in the control group (Table 1). As expected, there was a greater proportion of obesity among patients with DM compared to controls. Also, smokers were seen in 5.8% of the DM group compared to 6.8% in the control group.

Table 1 shows the distribution of pancreatic, gallbladder, and extrahepatic biliary cancers in case and control groups. The frequency of gallbladder cancer was 0.03% among patients with diabetes and there were no patients detected with gallbladder cancer in the control group. Extrahepatic biliary cancer was also five times more common in patients with diabetes when compared to control patients, 0.1% *vs* 0.02%, respectively. Pancreatic cancer in subjects with diabetes (0.9%) was three times more common when compared to control subjects (0.3%).

The occurrence of other biliary and pancreatic disorders is also depicted in Table 1 in both groups, as some of these disorders are potential risk factors for biliary or pancreatic cancer. Cholelithiasis was observed more commonly in DM patients (4.5%) in comparison to controls (2.8%). In addition, cholecystitis, sclerosing cholangitis and other

**Table 1** Demographics and predictive factors in diabetes mellitus (DM) patients and controls (%)

Variable	Diabetes (n = 278 761)	Controls (n = 836 283)	P value
Age ± SD (yr)	65.8 ± 11.3	64.8 ± 12.7	NS
Male sex	97.8	97.4	< 0.001
Caucasian	65.3	68.3	< 0.001
Obesity	15.7	7.5	< 0.001
Smoking	5.8	6.8	< 0.001
Gallbladder cancer	0.03	0	< 0.001
Extrahepatic biliary cancer	0.1	0.02	< 0.001
Pancreatic cancer	0.9	0.3	< 0.001
Pancreatitis	5.1	2.7	< 0.001
Cholelithiasis	4.5	2.8	< 0.001
Choledocholithiasis	0.8	0.5	< 0.001
Cholecystitis	0.9	0.5	< 0.001
Sclerosing cholangitis	0.4	0.2	< 0.001
Other biliary diseases	1.2	0.6	< 0.001
Other pancreatic disease	1.7	0.3	< 0.001

**Table 3** Pancreatic diseases associated with DM: univariate and multivariate analysis

Variables	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age > 50 yr	1.51 (1.49-1.54)	< 0.001	1.51 (1.53-1.57)	< 0.001
Male sex	1.18 (1.14-1.22)	< 0.001	1.09 (1.06-1.22)	< 0.001
Caucasian	0.86 (0.85-0.87)	NS	0.91 (0.90-0.92)	NS
Smoking	1.16 (1.14-1.19)	< 0.001	0.99 (0.95-1.02)	NS
Obesity	2.30 (1.70-3.10)	< 0.001	2.68 (2.62-2.75)	< 0.001
Pancreatic cancer	2.48 (2.26-2.72)	< 0.001	3.22 (3.03-3.42)	< 0.001
Cholelithiasis	1.66 (1.62-1.70)	< 0.001	1.94 (1.89-1.98)	< 0.001
Choledocholithiasis	1.52 (1.44-1.62)	< 0.001	1.82 (1.72-1.93)	< 0.001
Pancreatitis	1.98 (1.94-2.03)	< 0.001	2.30 (2.25-2.36)	< 0.001
Other pancreatic disorders	5.16 (4.88-5.45)	< 0.001	6.15 (5.82-6.50)	< 0.001

biliary diseases occurred more commonly in diabetic patients. Furthermore, other pancreatic diseases were significantly higher in patients with diabetes when compared to controls (1.7% *vs* 0.3%, respectively).

Table 2 illustrates our first model of multivariate logistic regression, which analyzed gallbladder and extrahepatic biliary cancer in relation to DM. The presence of gallstone disease, smoking, and obesity were controlled for in both groups before the ORs were calculated. We found that gallbladder and extrahepatic biliary cancer was significantly and independently associated with DM with an OR and 95% CI of 2.20 (1.56-3.00) and 2.10 (1.61-2.53), respectively. Included in Table 2 are the associations between diabetes and other biliary diseases, which were accounted for to eliminate potential confounding factors. The presence of DM was found to be associated with cholelithiasis and other biliary disorders. (OR, 1.81; 95% CI, 1.77-1.85 and OR, 2.10; 95% CI, 1.86-2.36, respectively).

Table 3 demonstrates our second model of multivariate analysis, which examined the association between diabetes and the incidence of pancreatic cancer. The results were obtained after controlling for recognized risk factors, such as smoking, obesity, pancreatitis, and other pancreatic disorders. After all case and control patients

**Table 2** Gallbladder diseases associated with DM: univariate and multivariate analysis

Variables	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age > 50 yr	1.51 (1.49-1.54)	< 0.001	1.56 (1.54-1.580)	< 0.001
Gender M	1.18 (1.15-1.22)	< 0.001	0.80 (0.75-0.85)	NS
Race W	0.86 (0.85-0.87)	NS	0.75 (0.69-0.79)	NS
Smoking	1.16 (1.14-1.19)	< 0.001	0.86 (0.84-0.88)	NS
Obesity	2.30 (1.70-3.10)	< 0.001	2.52 (2.47-2.58)	< 0.001
Gallbladder cancer	2.01 (1.47-2.76)	< 0.001	2.20 (1.56-3.00)	< 0.001
Extrahepatic biliary cancer	1.81 (1.44-2.27)	< 0.001	2.10 (1.61-2.53)	< 0.001
Cholelithiasis	1.66 (1.62-1.70)	< 0.001	1.81 (1.77-1.85)	< 0.001
Choledocholithiasis	1.52 (1.44-1.62)	< 0.001	1.47 (1.43-1.50)	< 0.001
Cholecystitis	1.97 (1.87-2.08)	< 0.001	2.25 (2.02-2.52)	< 0.001
Sclerosing cholangitis	1.93 (1.78-2.10)	< 0.001	2.37 (1.76-3.12)	< 0.001
Other biliary diseases	1.99 (1.90-2.09)	< 0.001	2.10 (1.86-2.36)	< 0.001

were considered, a significant relationship between diabetes and pancreatic cancer was established (OR, 3.22; 95% CI, 3.03-3.42). Diabetes was also associated with pancreatitis and other pancreatic disorders with an OR of 2.30 (95% CI, 2.25-2.36) and 6.15 (95% CI, 5.82-6.50).

## DISCUSSION

Type 2 DM is one of the most common and challenging problems faced today because of the many complications that result from this disease. Approximately 140 million people worldwide currently have diabetes, and this number is projected to reach up to 300 million by the year 2025<sup>[15]</sup>. The massive prevalence of this disease may now be unmasking additional, yet to be discovered, complications such as pancreatic and biliary cancer. A recent study has revealed a relationship between increasing fasting serum glucose and the incidence of gastrointestinal malignancies in Korean men and women<sup>[16]</sup>.

Pancreatic cancer is the fifth leading cause of cancer-related mortality in the United States<sup>[17,18]</sup>. The incidence of pancreatic cancer is higher among men and African Americans<sup>[18,19]</sup>. Previous studies have documented risk factors for the development of pancreatic cancer<sup>[6-8]</sup>. The most well-established risk factors for pancreatic cancer are smoking, genetic predisposition, chronic pancreatitis, and DM. A recent study has shown an increase in the incidence of pancreatic cancer among overweight patients, and that moderate exercise is associated with a lower incidence of pancreatic cancer<sup>[20]</sup>.

The linkage between pancreatic cancer and diabetes is well recognized. However, it has been debatable whether diabetes is a risk factor for, or a consequence of, pancreatic cancer. Earlier studies could not address this question adequately because the presence of type 2 diabetes has not been documented before the onset of disease. A more recent meta-analysis has shown that a history of diabetes for  $\geq 5$  years increases the incidence of pancreatic cancer by twofold<sup>[21]</sup>. In a hospital based case-control study, Bonelli *et al*<sup>[22]</sup> have demonstrated that the risk of pancreatic cancer was increased by 6.2-fold in patients with diabetes, which necessitated insulin therapy

for > 5 years. Our study supported these findings by showing that the occurrence of pancreatic cancer was increased by threefold in DM patients when compared to controls.

Primary carcinoma of the gallbladder is the fifth most common malignancy of the gastrointestinal tract in the United States. Approximately 5000-6000 adults are diagnosed annually, and most will die within 1 year of diagnosis<sup>[23,24]</sup>. Although the etiology of primary gallbladder carcinoma is not well understood, several factors have been postulated to place patients at a greater risk. These risk factors include gallstone disease, obesity, female sex, tobacco use, and an anomalous pancreaticobiliary ductal union<sup>[24,25]</sup>. Perhaps no risk factor has been attributed to gallbladder cancer more than gallstone disease, but the relationship between diabetes and gallbladder cancer has not been established conclusively. However, there has been one previous population-based study that showed an excess risk for all biliary cancers in patients with diabetes<sup>[5]</sup>.

This is one of the first studies to demonstrate a clear association of diabetes with gallbladder and extrahepatic biliary cancer. In our study, patients with diabetes had a twofold increased risk of having gallbladder or extrahepatic biliary cancer after controlling for known risk factors.

Our understanding of DM has changed dramatically over the past few years. Initially thought of as a disease secondary to a lack of insulin production, type 2 DM is now recognized as an ailment of insulin resistance and resultant hyperinsulinemia. First-line therapy now specifically targets insulin-mediated glucose utilization in the liver and peripheral tissue<sup>[26,27]</sup>. The over-production of both insulin and insulin-like growth factors (IGFs) has been postulated to increase carcinogenesis and may have played an essential role in the development and progression of pancreatic and biliary cancer in our patients with diabetes<sup>[28]</sup>. It would be of great interest to see whether there is a trend towards a greater risk for pancreatic and gallbladder cancer among diabetics with an increasing degree of hyperinsulinemia.

Evidence from animal and human studies has suggested that abnormal glucose metabolism plays an important role in pancreatic carcinogenesis<sup>[29,30]</sup>. Recent evidence supports the suggestion that insulin and IGF-1 act through a tyrosine kinase growth factor cascade in enhancing tumor cell proliferation.

Another contributor to this problem might be the rising prevalence in all age groups of the metabolic syndrome, specifically insulin resistance, in the United States<sup>[31]</sup>. The metabolic syndrome is associated with a chronic inflammatory state with accompanying cytokine abnormalities, which could also contribute to tumor progression. Furthermore, diabetic patients are at a higher risk for developing gallstones, which have also been recognized as a risk factor for the development of gallbladder and other biliary cancers<sup>[32]</sup>.

The strength of our study was that it encompassed a large patient population, dramatically more than any other study that has examined this association. This

approach allowed for a large sample of diabetics in the VA population, thereby increasing the overall power of the study.

The weakness of our study was that the population we studied was restricted to the VA population and therefore was composed mainly of men. Obtaining a larger female sample could have been helpful in allowing us to observe any differences in the associations according to sex. Other limitations to our study were the potential for misclassification bias (errors in cancer diagnosis ICD9-CM code classification) and cancers diagnosed post mortem. However, given the large size of our patient population, the significance of misclassification and post mortem cancer diagnosis were thought to be inconsequential toward the overall study results. Also, because of our current dearth of knowledge regarding the development of biliary and pancreatic malignancies, our results might have been affected by unknown confounding factors. However, our study did address the known risk factors for these malignancies and controlled for these so that they would not affect our overall results.

In summary, we found that type 2 DM was associated with an increased risk of gallbladder, biliary and pancreatic cancer, independent of other known risk factors such as cholelithiasis, pancreatitis, obesity and smoking. This information should further heighten our awareness of the many complications associated with insulin resistance and modify the intensity of our approach to these patients. This could warrant a keener eye by the primary care physician for any abnormalities in his or her diabetic patients, which indicate the possibility of cardiovascular, renal and ophthalmic complications, as well as the rare but foreseeable possibility of a fatal pancreaticobiliary malignancy.

## COMMENTS

### Background

The prevalence of type 2 diabetes mellitus (DM) is growing globally and has become a major public health problem that is approaching epidemic proportions worldwide. This disease has been associated with several cancers, most notably of the liver, endometrium, kidney and pancreas. To the best of our knowledge, the relationship of DM with gallbladder and extrahepatic biliary cancers has not been reported clearly in the literature.

### Research frontiers

It is of great significance to investigate the relationship between type 2 DM and gastrointestinal malignancies from an epidemiological standpoint, to determine preventive measures and implement screening strategies.

### Innovations and breakthroughs

Distinct from most previous studies that have involved a limited sample size or a specified cancer site, we conducted a comprehensive assessment of the risk of gallbladder, biliary and pancreatic malignancies in a large cohort of patients with DM.

### Applications

Type 2 DM poses an increased risk of gallbladder, biliary and pancreatic cancer, independent of other known risk factors such as cholelithiasis, pancreatitis, obesity and smoking. This information heightens awareness of the many complications associated with insulin resistance and should modify the intensity of our approach to these patients. This warrants a keener eye by primary care physicians for any abnormalities in their diabetic patients, which indicate the possibility of cardiovascular, renal and ophthalmic complications, as well as the rare but foreseeable possibility of a fatal pancreaticobiliary malignancy.

### Terminology

Type 2 DM is associated with an increase in the occurrence of gallbladder,



biliary and pancreatic cancer among American veterans, independent of other known risk factors.

### Peer review

The study deals with an interesting epidemiological analysis of the question if DM is a risk factor for several gastrointestinal cancers. It reports associations between type 2 DM and incidence of certain cancers.

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