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Probability of Pancreatic Cancer Following Diabetes: A Population-Based Study

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Abstract

Background & Aims—Although diabetes occurs frequently in pancreatic cancer, the value of new-onset diabetes as a marker of underlying pancreatic cancer is unknown.

Methods—We assembled a population-based cohort of 2122 Rochester, Minnesota, residents age ≥ 50 years who first met standardized criteria for diabetes between January 1, 1950, and December 31, 1994, and identified those who developed pancreatic cancer within 3 years of meeting criteria for diabetes. We compared observed rates of pancreatic cancer with expected rates based on the Iowa Surveillance Epidemiology and End Results registry. In a nested case control study, we compared body mass index (BMI) and smoking status in diabetes subjects with and without pancreatic cancer.

Results—Of 2122 diabetic subjects, 18 (0.85%) were diagnosed with pancreatic cancer within 3 years of meeting criteria for diabetes; 10 of 18 (56%) were diagnosed < 6 months after first meeting criteria for diabetes, and 3 were resected. The observed-to-expected ratio of pancreatic cancer in the cohort was 7.94 (95% CI, 4.70–12.55). Compared with subjects without pancreatic cancer, diabetic subjects with pancreatic cancer were more likely to have met diabetes criteria after age 69 (OR = 4.52, 95% CI, 1.61–12.74) years but did not differ significantly with respect to BMI values (29.2 ± 6.8 vs 26.5 ± 5.0 , respectively). A larger proportion of those who developed pancreatic cancer were ever smokers (92% vs 69%, respectively), but this did not reach statistical significance.

Conclusions—Approximately 1% of diabetes subjects aged ≥ 50 years will be diagnosed with pancreatic cancer within 3 years of first meeting criteria for diabetes. The usefulness of new-onset diabetes as marker of early pancreatic cancer needs further evaluation.

Pancreatic cancer patients seldom exhibit disease-specific symptoms until the cancer is at an advanced stage. If the tumor is to be discovered early, it will have to be done in asymptomatic individuals. A number of formidable obstacles limit the ability of health care providers to screen for pancreatic cancer. One of them is lack of a high-risk population for sporadic pancreatic cancer. Currently, rare genetic syndromes with a high incidence of pancreatic cancer are being targeted for screening using endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography.¹⁻³

To make headway in screening for sporadic pancreatic cancer, efforts to define populations at high risk for having or developing sporadic pancreatic cancer will have to develop *pari passu* with advances in imaging studies and identification of novel biomarkers. In this study, we highlight the potential for utilizing hyperglycemia and diabetes to define a population at high

risk for having pancreatic cancer. We also discuss the limitations of this and other studies and provide insights into why we believe hyperglycemia and diabetes may be markers of “early” pancreatic cancer and what studies need to be done to prove this hypothesis.

The association between diabetes and pancreatic cancer has long been recognized. However, the assessment of diabetes as a clinically relevant screening target for pancreatic cancer is complicated by the fact that, although long-standing diabetes is an etiologic factor for pancreatic cancer, new-onset diabetes is a manifestation of the cancer. Although most studies show an elevated risk of pancreatic cancer among persons with long-standing diabetes, the strength of this association is modest at best.⁴ In a meta-analysis of 20 epidemiologic studies, the pooled relative risk of pancreatic cancer for those whose diabetes was diagnosed at least 1 year prior to either diagnosis of pancreatic cancer or to pancreatic cancer death was 2.1 (95% CI: 1.6–2.8).⁴ Many, but not all, cohort studies reveal that the risk of pancreatic cancer associated with diabetes decreases with increasing duration of follow-up.^{5–9} Additionally, although the number of persons with pancreatic cancer in the population is small, the number of older persons with long-standing diabetes is large. Thus long-standing diabetes as a marker for pancreatic cancer is likely to have limited clinical utility.

There is increasing evidence to support the notion that diabetes may be a consequence of pancreatic cancer. Diabetes and hyperglycemia are present in up to 80% of pancreatic cancer, ^{10–13} are usually of recent onset,^{13–21} and improve or remit after resection of cancer.²¹ Based on such observations, new-onset diabetes has been suggested as a possible target for screening for pancreatic cancer.^{11,15–17,22} However, it is important to recognize that previous epidemiologic studies of the association between diabetes and pancreatic cancer are generally uninformative about the clinical utility of newly identified diabetes as a marker for pancreatic cancer. In almost all case control studies, duration of diabetes is unclear because it was assessed by self- or proxy report. Three studies have used postload glucose levels at baseline, and persons with and without prevalent diabetes have been followed forward for pancreatic cancer.^{23–25} However, these studies are relatively uninformative regarding the short-term risk of pancreatic cancer associated with diabetes because the mean age was relatively young,^{23,24} and there were very few pancreatic cancer deaths within the first 5 years among persons with diabetes at baseline.^{23,24}

To assess the potential benefit of screening for pancreatic cancer among subjects with newly identified diabetes, population-based cohort studies are needed. In previous studies, estimates of the prevalence of newly diagnosed diabetes among controls do not afford estimates of the prevalence of newly diagnosed diabetes in the population. This limitation also applies to cohort studies in which the study population is limited to persons with prevalent diabetes who are not necessarily representative of persons with diabetes in the population generally (ie, hospitalized diabetes cases or patients of a diabetes clinic). Thus, there is a need for studies that afford estimates of both the number of newly diagnosed cases of diabetes that exist within the population and of the excess risk of pancreatic cancer associated specifically with newly identified diabetes.

Our study used the longitudinal, population-based resources of the Rochester Epidemiology Project (REP)²⁶ to identify all Rochester, Minnesota, residents who first met standardized research criteria for diabetes on or after age 50 years between January 1, 1950, and December 31, 1994. In this cohort, we determined the likelihood of pancreatic cancer diagnosis within 3 years of meeting criteria for diabetes and compared observed rates with those expected for persons of similar age and sex distribution. Among persons with diabetes, we compared those with and without pancreatic cancer for other known or potential risk factors, ie, age, sex, smoking, and body mass index (BMI).

Patients and Methods

The study was approved by the Mayo Foundation Institutional Review Board (IRB). Population-based studies are possible in Rochester, Minnesota, because essentially all medical care received by local residents is delivered by the Mayo Clinic and the Olmsted Medical Center. Since 1907, every Mayo Clinic patient has been assigned a unique identifier. All information from every contact (including hospital inpatient or outpatient care, office visits, emergency room, and nursing home care, as well as death certificate and autopsy information) is contained within a single dossier for each patient, and diagnoses assigned at each visit are entered into computer files. Under the auspices of the Rochester Epidemiology Project (REP), this diagnostic index and medical records linkage were expanded to include the other providers of care to local residents,²⁶ thus providing a comprehensive medical database of the Rochester population.

Rochester Diabetes Incidence Cohort

REP resources were used to construct the Rochester diabetes incidence cohort.²⁷⁻²⁹ The full cohort includes all 2151 individuals who first met research criteria for diabetes as a Rochester resident between 1950 and 1995. In constructing this cohort, confirmation of diabetes status was based on review of provider-linked medical records by trained nurse abstractors, under the direction of an endocrinologist. Records were reviewed from date of first contact with each REP provider until date of last contact, death, or end of the study period for all laboratory glucose values and evidence of any antidiabetic medication. Laboratory glucose values are available within REP medical records for 1930 through the present. Glycemic criteria approximated National Diabetes Data Group (NDDG) recommendations,³⁰ ie, 2 consecutive fasting glucose levels ≥ 140 mg/dL (7.8 mmol/L) or both 1- and 2-hour levels ≥ 200 mg/dL (11.1 mmol/L) obtained during a standard oral glucose tolerance test. Adjustments were made for changes in laboratory methods over time.³¹ Individuals who failed to meet glycemic criteria but who used oral agents or insulin for at least 2 weeks or until death also qualified as cases.

Because it was not feasible to review manually all medical records for every Rochester resident over this 45-year period, the review was limited to candidate cases, ie, all residents with any diagnosis suggestive of diabetes (eg, elevated blood glucose, impaired glucose tolerance, diabetes mellitus, rule-out diabetes, diabetic nephropathy) in the REP diagnostic index. In a previous study of all Rochester residents who died on or after age 45 years in 1970–1995, the median number of years of medical records available for review (ie, time from first contact with a REP provider until death) was 43 years (inter-quartile range, 24–58 years), and over 25% of all decedents had a diagnosis in the REP diagnostic index that qualified them as a candidate case for the diabetes incidence cohort.²⁹ It has also been demonstrated that essentially all Rochester residents have contact with at least 1 REP provider in any 5-year period.²⁶ In each year, the proportion of local residents age ≥ 30 years who have at least 1 blood glucose measurement averages approximately 37% for males and 44% for females.²⁷

The present study was limited to individuals who first met criteria for diabetes between January 1, 1950, and December 31, 1994, on or after age 50 years and who were residing in Rochester for at least 1 year as of the date they first met criteria (ie, incident cases) (Figure 1). In accordance with a Minnesota statute,³² 24 individuals who declined to authorize the use of their medical records in the research were excluded from the study. Thus, there were 2127 authorized and eligible incident diabetes cases (Figure 1).

Ascertainment of Incident Pancreatic Cancers

The list of 2127 incident diabetes cases was cross matched with the diagnostic index maintained by the REP to identify those with any diagnosis of pancreatic adenocarcinoma within 3 years

of meeting criteria for diabetes ($n = 27$). After review of the medical records of these 27 subjects, 9 were excluded (5 who were found to have developed diabetes after pancreatectomy or cancer and 4 who were found to not have pancreatic ductal adenocarcinoma) (Figure 1).

Selection of Controls for Nested Case Control Study

For each of the 18 remaining diabetes cases who met criteria for pancreatic ductal adenocarcinoma, 4 members of the diabetes cohort were identified who were of same sex, similar year of birth, and similar year in which criteria for diabetes were met, but for whom there was no diagnosis of pancreatic cancer.

Statistical Analyses

Incidence and risk of pancreatic cancer in the diabetes cohort—The incidence of pancreatic cancer among members of the cohort was calculated as the ratio of observed cases to the number of diabetes person-years of follow-up. Diabetes person-years were calculated from the date that all 2122 members of the diabetes cohort first met criteria for diabetes, until the earliest of pancreatic cancer diagnosis, death, or 3 years.

The excess risk of pancreatic cancer within 3 years of first meeting criteria for diabetes mellitus was estimated by comparing the observed number of cases among members of the diabetes incidence cohort to the expected number of cases in the general population. The expected number was estimated by multiplying the number of diabetes person-years for each 5-year age group and sex by the corresponding age- and sex-specific incidence rates from data from the Surveillance, Epidemiology, and End Results (SEER) program.³³ The incidence of pancreatic cancer in Olmsted county has been reported.³⁴ The study by Riela et al³⁴ showed that the incidence of pancreatic cancer in Olmsted county is very similar to the incidence of pancreatic cancer in the Iowa SEER population. However, the study by Riela et al³⁴ did not cover the entire period of our study, and the number of patients diagnosed with pancreatic cancer each year is small. We therefore chose to use the Iowa SEER data because Iowa is the nearest state with SEER data available in the United States, and the demographics of Iowa are very similar to those of Rochester, Minnesota.

Risk ratios (defined as the ratio of observed to expected number of cases of pancreatic cancer) and 95% confidence intervals (based on the Poisson distribution of the observed number of pancreatic cancer cases) were estimated, both overall and for subgroups (ie, ages <70 vs ≥ 70 years; male vs female).³⁵

Nested case control study—To evaluate whether there was an association between smoking or BMI and pancreatic cancer among persons with diabetes, the analysis included the 4 diabetes controls for each case, for a total of 72 controls and 18 cases.³⁶ The medical records of these 90 individuals were reviewed for smoking history, classified as ever, never, or unknown. BMI (weight in kilograms/height in meters²) as of the date criteria for diabetes were met (± 2 years) was noted. To obtain risk ratios and 95% confidence intervals, we employed conditional logistic regression, matching on age and sex. Statistical analyses were conducted using Statistical Analysis Software (SAS) version 8 (SAS Institute, Cary, NC).

Results

Between January 1, 1950, and December 31, 1994, there were 2122 Rochester residents ≥ 50 years of age who first met National Diabetes Data Group (NDDG) criteria for diabetes (male, 50%; mean age, 66.2 ± 10.1 years). Persons were followed to the earliest of pancreatic cancer diagnosis, death, or 3 years, for a total of 5799 person-years of follow-up in the diabetes cohort; during which time, 18 subjects (0.85%) met criteria for pancreatic cancer.

Characteristics of Diabetes Associated With Pancreatic Cancer

There was no family history of diabetes in 11 of 18 (61%) subjects; 3 had siblings with diabetes and 1 each had a parent and uncle with diabetes. Data on family history were not available in 2 patients. Seven (39%) subjects were treated with insulin and 3 with oral hypoglycemics; the remaining subjects were not on hypoglycemic medications. At the time patients met criteria for diabetes, 9 of 18 had cancer-related symptoms, 2 had diabetes-related symptoms (polydipsia and polyphagia), and the remaining had no symptoms or were being investigated for an unrelated problem (eg, atrial fibrillation).

Characteristics of Pancreatic Cancer Associated With Diabetes

Twelve of 18 (67%) subjects were males (Table 1). Their mean age at cancer diagnosis was 72.3 ± 8.1 years. On average, pancreatic cancer was identified 6.6 ± 7.7 months after the date diabetes criteria were met. In 10 of 18 (56%), the cancer was diagnosed <6 months after first meeting criteria for diabetes. The cancer was resected in 3 and was unresectable in the remaining patients.

Incidence and Risk of Pancreatic Cancer in the Diabetes Cohort

The crude 3-year incidence of pancreatic cancer among persons with diabetes ≥ 50 years of age was 310/100,000 person-years (Table 2). When compared with expected rates based on the Iowa SEER data, the overall observed to expected ratio of pancreatic cancer was 7.94 (95% CI: 4.70–12.55) (Table 2). Subgroup analyses showed that the incidence of pancreatic cancer was significantly increased in all age- and sex-matched subgroups, although it was more pronounced in subjects ≥ 70 and in males (Table 2).

Characteristics Associated With Pancreatic Cancer Among Persons With Diabetes

Compared with diabetes cases without pancreatic cancer, those with pancreatic cancer were more likely to have first met criteria for diabetes on or after age 70 years (OR = 4.52, 95% CI: 1.61–12.74). The 2-fold difference in sex did not reach statistical significance (OR for male sex = 2.01, 95% CI: 0.75–5.38).

In the nested case control analysis, smoking data were available on a similar proportion of pancreatic cancer cases and controls (13 of 18 = 72.2% vs 55 of 72 = 76.4%, respectively, $P = .76$). Of those with smoking data, 12 of the 13 pancreatic cancer cases (92.3%) were ever smokers compared with 38 of the 55 controls (69.1%) (OR = 5.37, 95% CI: 0.65–44.66, $P = .16$). In conditional logistic regression analysis, the odds ratio for smoking was 5.84 (95% CI: 0.62–55.43). Although pancreatic cancer cases were on average overweight at the time of meeting criteria for diabetes (BMI, 26.50 ± 4.97), their BMI values did not differ significantly from those of subjects without pancreatic cancer (29.23 ± 6.82 , $P = .10$). When both BMI and smoking were included in the model, estimated odds ratios were 0.86 (95% CI: 0.72–1.02) and 8.53 (95% CI: 0.67–108.25), respectively.

Discussion

In this population-based study, 18 of 2122 (0.85%) diabetes subjects who first met criteria for diabetes ≥ 50 years of age were identified with pancreatic cancer within 3 years of meeting criteria for diabetes. This represents a 3-year incidence nearly 8 times that for the general population. Forty-four percent of pancreatic cancer subjects in the cohort met criteria for diabetes ≥ 6 months before the diagnosis of the cancer.

The strengths of the present study are that it was population-based, the diagnosis of pancreatic cancer was ascertained with a high degree of certainty in all subjects, subjects without ductal adenocarcinoma of the pancreas were carefully excluded, all individuals within the population

who met research criteria for diabetes during the study period were included, and the criteria for diabetes were uniformly applied throughout the study period.

The study is limited in that ascertainment of diabetes case status in the REP diabetes incidence cohort was based on retrospective review of medical records and laboratory glucose values. Individuals who never met NDDG criteria but who did meet the more recently introduced American Diabetes Association criteria of fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L)³⁰ are not included. Neither are individuals who would have met NDDG criteria if tested prospectively but who never received a diagnosis of diabetes or diabetes-like condition while a local resident. However, diabetes is a chronic disease, and, for the reasons outlined above (see Materials and Methods section), we believe that the extended passive surveillance for diabetes afforded by the REP is relatively complete, especially for individuals who meet NDDG criteria. The surveillance afforded by REP resources is advantaged over studies that prospectively measure glucose values on a volunteer sample of the population³⁷ because such studies are likely to miss frail elderly individuals, all of whom are included in our passive surveillance.

Our study provides population-based epidemiologic evidence to show that, in subjects with new-onset diabetes, there is a high prevalence of pancreatic cancer. Recent studies^{38,39} show an even higher prevalence of pancreatic cancer in subjects with new-onset diabetes (5.2% to 13.6%) because they targeted selected high-risk subjects with recently diagnosed diabetes. These studies and the earlier epidemiologic studies suggest that subjects with new-onset diabetes are a high-risk group for having pancreatic cancer.

However, the short interval between diagnosis of diabetes and diagnosis of pancreatic cancer and the low rate of resectability raises the question of whether diabetes is a marker of “early,” resectable, pancreatic cancer. Because our population was neither screened for diabetes nor for pancreatic cancer, the benefit of screening for pancreatic cancer using diabetes or hyperglycemia as a marker cannot be answered by the present study and deserves a prospective analysis. Based on the results of our recent study,⁴⁰ it appears that diagnosis of pancreatic cancer even 6 months before clinical diagnosis could have a significant impact on resectability. In our study, in 44% of cases, the patients met criteria for diabetes ≥ 6 months prior to diagnosis of cancer. Would screening for cancer at the time they met criteria for diabetes have led to detection of resectable cancer?

Lessons critical to using hyperglycemia as a marker of pancreatic cancer can be learned from our experience as well as that of other investigators. Pancreatic cancer patients seldom exhibit disease-specific symptoms until late in the course of the disease, and pancreatic cancer patients with diabetes are no exception. In our study as well as the other recent studies,^{38,39} patients with new-onset diabetes were investigated for cancer mostly after development of cancer symptoms (eg, abdominal pain, weight loss, and jaundice). The poor rate of resectability in all these studies shows that the strategy to use symptoms such as jaundice and anorexia as clues to suspect pancreatic cancer in new-onset diabetes is unlikely to detect resectable cancer because these symptoms generally are associated with unresectable pancreatic cancer.^{38,39}

Studies in which early and resectable cancers have been screened for hyperglycemia show that glucose intolerance occurs at an early stage of pancreatic cancer and is not dependent on size of tumor or stage of disease. Tsuchiya et al⁴¹ reported that 48 of 79 (60.8%) patients with small pancreatic cancers (<20 mm in size) had abnormal glucose tolerance. We¹³ and others^{10,11} have reported that 55%–65% of patients with resectable pancreatic cancer have glucose intolerance and diabetes. Permert et al¹¹ reported that 64% of patients with resectable tumors had diabetes upon formal glucose tolerance testing. In our series, although 12 of 22 (55%) patients with resectable cancer had diabetes, 40 of 108 (37%) of patients with unresectable

disease had diabetes ($P = \text{ns}$). Animal studies also show that development of glucose intolerance coincides with appearance of visible pancreatic tumors in hamsters.⁴²

Because glucose intolerance occurs early in pancreatic cancer and there is ~1% prevalence of pancreatic cancer in subjects with new-onset diabetes, hyperglycemia is an attractive biomarker for a high-risk group for pancreatic cancer. On the other hand, if pancreatic cancer in new-onset diabetes is usually unresectable, is it worthwhile pursuing hyperglycemia as a marker of early cancer? Understanding the reasons for the discordance between the high prevalence of diabetes in patients diagnosed with resectable and small cancers and low resectability in patients with new-onset diabetes will help design future studies to answer conclusively the question of usefulness of hyperglycemia as a marker of early cancer.

In studies on prevalence of cancer in new-onset diabetes, including ours, patients with physician-diagnosed diabetes were investigated for cancer mostly after development of cancer symptoms. On the other hand, in studies showing a very high prevalence of diabetes in early pancreatic cancer, subjects with resectable and small pancreatic cancers were screened for diabetes. Because in a majority of pancreatic cancer patients with diabetes, the diabetes remains undiagnosed, studies screening for diabetes have a much higher prevalence of diabetes in pancreatic cancer. In an earlier study,¹³ we showed that the diagnosis of diabetes was made at the same time as the diagnosis of pancreatic cancer in 46% of patients (mostly because we were screening for it) and in another 10% in 1 month prior to cancer diagnosis while being investigated for cancer symptoms. This is not totally unexpected. In type 2 diabetes, the onset of diabetes occurs at least 4–7 years before clinical diagnosis,⁴³ and one third of prevalent cases of type 2 diabetes in the population are undiagnosed.⁴⁴ In pancreatic cancer, the prevalence of undiagnosed diabetes is even higher (~50%) because the cancer manifests itself before the diabetes can become symptomatic.

We believe that for hyperglycemia to be a clinically useful marker of early cancer one will have to screen *asymptomatic* individuals for hyperglycemia. However, type 2 diabetes is common in the elderly population and pancreatic cancer relatively rare. The success of the strategy to use hyperglycemia as a screening tool to identify subjects with a high likelihood of having underlying undiagnosed pancreatic cancer will depend largely on our ability to differentiate pancreatic cancer-induced diabetes from type 2 diabetes using a serologic marker. Although a biomarker for pancreatic-induced diabetes is yet to be identified, laboratory and clinical evidence suggests that diabetes induced by pancreatic cancer may be humorally mediated. Cell culture supernatants from pancreatic cancer cell lines induce glucose intolerance in SCID mice. In humans, resection of pancreatic cancer leads to amelioration or remission of diabetes.²¹ The report by Basso et al⁴⁵ that a peptide with m/z 2030 may be a putative diabetogenic factor in pancreatic cancer suggests that a serologic marker of diabetes induced by pancreatic cancer may be identified in the near future.

Identifying clinical characteristics that point to diabetes induced by pancreatic cancer rather than type 2 diabetes would also help in enriching the pool of newly diagnosed diabetes subjects for pancreatic cancer. In our study, we compared diabetes subjects with and without pancreatic cancer for other known or potential risk factors, ie, smoking and BMI. Smoking history data were available for only 13 of the 18 cases of pancreatic cancer in our study. Although 92% of the 13 diabetic subjects identified with pancreatic cancer were ever smokers, this was not statistically different from the proportion of smokers among diabetic individuals without pancreatic cancer (69%). We were unable to quantify the degree of smoking exposure (ie, pack-years). The value of detailed smoking history in defining a high-risk population for having pancreatic cancer among subjects with newly diagnosed diabetes needs additional study.

Obesity has been associated with a small but significant increase in risk of pancreatic cancer.⁴⁶ In our study, diabetic subjects who were subsequently diagnosed with pancreatic cancer tended to be overweight at the time they met criteria for diabetes. This is similar to our earlier observation that pancreatic cancer subjects, especially those with diabetes, were overweight before the onset of weight loss.¹³ However, because type 2 diabetes is also associated with obesity, it is perhaps not surprising that the BMI of diabetic subjects without a diagnosis of pancreatic cancer was not different from that of diabetic subjects who had pancreatic cancer.

In conclusion, a small (0.85%) but important segment of the population of elderly subjects with new-onset diabetes has pancreatic cancer as the basis for this presentation. This translates to a 3-year risk of pancreatic cancer of nearly 8 times higher than that for a person of similar age and sex in the general population. However, further study is required before hyperglycemia and diabetes can be used as clinically relevant markers of undiagnosed pancreatic cancer.

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Abbreviation used in this paper

REP

Rochester Epidemiology Project

Figure 1.
Flow of and relationship of subjects in the Diabetes Incidence Cohort with this study.

Characteristics of the 18 Subjects With Pancreatic Cancer in the Rochester Diabetes Incidence Cohort

Table 1

Patient No.	Age (y) ^a	Sex	Interval (mo) ^b	Procedure to diagnose pancreatic cancer	BMI as of date diabetes criteria met	Smoking
1	66	M	<1	Laparotomy with biopsy	26.8	Ever
2	62	F	<1	Distal pancreatectomy	27.5	Ever
3	74	M	<1	Autopsy	24.1	Unknown
4	80	F	<1	Laparotomy, biliary bypass	35.6	Ever
5	89	M	<1	Laparotomy with biopsy	21.2	Unknown
6	70	F	<1	Pancreatico-duodenectomy	22.8	Never
7	72	M	1.3	Biopsy of liver metastases from pancreatic tail lesion	24.8	Ever
8	58	F	1.9	Laparotomy, biopsy of metastatic nodule	34.2	Ever
9	57	M	3.8	Laparotomy with biopsy	28.8	Ever
10	80	F	4.3	Biopsy of metastatic nodule	26.3	Unknown
11	71	M	6.3	Distal pancreatectomy	23.1	Ever
12	70	M	6.8	Laparotomy with biopsy	21.6	Unknown
13	73	M	6.8	Laparotomy with biopsy	21.3	Ever
14	81	F	11.1	Biopsy of pancreatic head mass	20.3	Ever
15	74	M	11.5	Laparotomy	33.1	Unknown
16	78	M	18.4	Autopsy	29.6	Ever
17	73	M	18.8	Biopsy of metastases	22.4	Ever
18	74	M	25.7	Laparotomy with biopsy	33.5	Ever

^a Age at diagnosis of pancreatic cancer.

^b Interval between date criteria for diabetes met and date of diagnosis of pancreas cancer.

Table 2
Observed and Expected Numbers of Pancreatic Cancers in the Diabetes Incidence Cohort Stratified by Age and Sex

Groups	Cases (n)		Incidence per 100,000	Observed/ expected ratio	95% Confidence interval
	Observed	Expected			
Overall					
Stratified by age					
<70 y	18	2.27	310	7.94	4.70–12.55
≥70 y	5	0.96	131	5.23	1.70–12.20
Stratified by sex					
Female	13	1.31	653	9.91	5.26–16.96
Male	6	1.03	206	5.83	2.14–12.68
	12	1.24	415	9.69	5.01–16.92