Diabetes mellitus and cancer risk in a population-based case–control study among men from Montreal, Canada

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Diabetics may have a higher risk of cancer, notably liver and pancreatic cancers. Evidence about other cancer types remains sparse. The authors examined potential associations between diabetes and several types of cancer in a large multicancer case–control project carried out in Montreal, Canada, in the 1980s. This report, based on 3,107 male cancer cases and 509 population controls, uses information on diabetes and several covariates collected by interview. Adjusted odds ratios (ORs) and 95% confidence intervals (CI) were estimated for the associations between diabetes and each of 12 cancer types. Risks of pancreatic and liver cancers were increased among diabetics: adjusted ORs were 2.1 (95% CI: 1.0, 4.3) for pancreatic and 3.1 (95% CI: 1.1, 8.8) for liver cancer. The increased risk of pancreatic cancer was completely restricted to those with recent onset of diabetes; this was likely a manifestation of reverse causality. Conversely, the increased risk of liver cancer was independent of the interval between diabetes and cancer diagnoses. No associations were observed with melanoma, non-Hodgkin's lymphoma, cancers of the esophagus, stomach, colon, rectum, lung, prostate, bladder and kidney. In conclusion, diabetes was associated with an increased risk of liver cancer among men, but with no other cancer type including pancreatic cancer.

Key words: diabetes mellitus; cancer; case–control; population-based

Diabetes mellitus is a common health condition. Its prevalence is estimated as 1.7 million cases in Canada[1] and 18.2 million cases in the U.S.,[2] one-third of which is undiagnosed. Diabetes prevalence has increased in the last decade,[3,4] in parallel with an increasing prevalence of obesity among children[5] and adults,[6,7] low levels of physical activity[8] and aging of the population. Diabetes is expected to remain as a major public health problem in the years to come.[9]

A link between diabetes and cancer has been investigated as far back as the early 20th century,[10] but remains controversial. The hypothesized biological mechanisms relate to the effect of insulin and insulin-like growth factors (IGFs) on cellular growth. Experimental evidence has suggested that both insulin and IGFs could stimulate tumoral cell proliferation.[11–13]

Among the epidemiological studies focusing on diabetes and cancer,[14–26] the most consistently reported associations were with liver and pancreatic cancers.[14,16,18–22,25,26] Several prior studies were based on cases ascertained from death records or cancer registries, and did not allow for adjustments for confounders other than age and sex.[14,15,19,21,23]

The purpose of the present study was to determine whether diabetes mellitus was associated with the subsequent risk of 12 types of cancer among men from Montreal, Canada, while adjusting for potentially confounding variables, and taking account of the temporal relationship between the diagnoses of diabetes and cancer.

Material and methods

Study design and population

The detailed methods of this population-based case–control study, originally designed to address occupational exposures and cancer risk among men, have been described elsewhere.[27,28] Briefly, Canadian men aged from 35 to 70 years and residing in the Montreal area were eligible to participate. Cases were ascertained from the major hospitals in Montreal, providing almost complete coverage (97%) of all incident cancer cases diagnosed between 1979 and 1985. Among the 4,576 eligible patients with histologically-confirmed primary incident cancer, a total of 3,730 (82%) cases were interviewed. Over 20 cancer types were included in the study. Results are presented here for 12 types with 30 or more cases: esophagus, stomach, colon, rectum, liver, pancreas, lung, prostate, bladder, kidney, melanoma and non-Hodgkin's lymphoma. Among the 740 potential population controls randomly sampled from electoral lists, 533 (72%) agreed to be interviewed. The study was approved by ethics committees at all participating institutions, and subjects provided informed consent.

Data collection

Information was collected during a questionnaire-based interview performed by a team of trained interviewers. If subjects were unavailable (deceased, too ill, or other), the interview was carried out with a close family member. Proxy respondents answered for 825 (22%) cancer patients and 67 (13%) controls. The proportion of proxy respondents varied according to cancer type. It was lowest in subjects with melanoma (12%), bladder (14%) and kidney cancers (14%), and highest among those with esophageal (32%), pancreatic (51%) and liver (60%) cancers. The information collected included sociodemographic characteristics; lifestyle factors such as frequency of use of selected dietary items, tobacco and alcohol consumption; self-reported current height and usual weight "when in good health"; and history of selected medical conditions.

Study subjects were asked if they had ever been diagnosed with diabetes; if yes, at what age and whether they took medication for this condition. Two sets of criteria were used to classify individuals as diabetic: (*i*) self-reported diabetes; (*ii*) self-reported diabetes plus self-reported use of medication for diabetes.

Statistical analyses

Analyses were restricted to subjects who completed a face-to-face interview, and provided information about diabetes, height and weight: 509 controls (95% of eligible) and 3,107 cancer patients (89% of eligible).

Abbreviations: AIC, Akaïke Information Criteria; BMI, body mass index; CI, confidence interval; GI, gastrointestinal; HCC, hepatocellular carcinoma; IGF, insulin-like growth factor; OR, odds ratio; SD, standard deviation.

Logistic regression was used to estimate the odds ratios (OR) and 95% confidence intervals (CI) for the association between diabetes and cancer, using separate regression models for each of the 12 cancer types. A basic set of covariates was entered in each model: age, family income, years of schooling, ethnicity, proxy status, and body mass index (BMI). For each cancer type, specific covariates were added in the fully adjusted model, such as smoking for smoking-related cancers.

BMI, in kilograms per meter square, was calculated from self-reported current height and usual weight. Different forms of the BMI variable were explored: continuous; binary (<25 and ≥ 25 kg/m^2); 3 categories (<20, 20 to <25 and ≥ 25 kg/m^2). The binary representation was selected, resulting in the best fit as judged by the Akaïke Information Criteria (AIC). Most models were adjusted for smoking. The cumulative exposure to cigarette smoking was estimated by multiplying the average number of cigarettes per day by the duration of smoking in years, expressed as "cigarette-years." Smoking was modeled with 3 variables: ever/never smoked, number of years since quitting if ex-smoker and natural log of "cigarette-years."[29] Other covariates were either continuous such as age, family income, and years of schooling; or categorical such as ethnicity (French Canadian; English Canadian; Italian, Jewish or other European; and other) and proxy status (self-respondent or proxy).

Results

Selected characteristics of population controls and cancer cases are shown in Table I. Population controls had a slightly higher income than that of most cancer groups, and were less likely to have ever smoked. As expected, the highest proportions of smokers were observed among subjects diagnosed with lung, esophageal and bladder cancer. The proportion of individuals with a BMI ≥ 25 was 58% among population controls, whereas in the case groups, it varied from 42% among those with stomach cancer to 60% in those with kidney cancer.

The proportions of diabetics based on 2 definitions are shown in Table II. Eight percent of the population controls reported being diabetic. In the cancer groups, the prevalence of self-reported diabetes varied from 4% among those with melanoma to 24% among liver cancer cases. Overall, approximately two-thirds of diabetics reported taking diabetes-related medication. The time interval between the diagnoses of diabetes and cancer varied according to cancer type. The median time since the diagnosis of diabetes was 5 years among population controls, and ranged from 1 year among subjects with pancreatic cancer to eleven years among bladder cancer cases. In the study sample, 7 subjects were diagnosed with diabetes before age 30, only 2 before age 20 (1 with kidney cancer, the other with lung cancer).

Adjusted ORs for the association between diabetes and cancer risk are shown in Table III. We observed a statistically significant excess of both liver and pancreatic cancers among diabetics. Exclusion of subjects whose information was provided by a proxy respondent, although producing less precise estimates, did not result in different patterns. When using the more stringent definition of diabetes, that is, also reporting medication use, the strength of these associations increased further. No convincing association was observed with the other cancer types.

Table IV shows the ORs for the associations between diabetes and liver and pancreatic cancers, stratified according to the interval between the 2 diagnoses. Subjects who reported having diabetes for 1 year or less were 10 times more likely to have pancreatic cancer than nondiabetics, but the association disappeared with longer intervals. By contrast, the increased risk of liver cancer was independent of the interval. For other cancer types, despite a few slightly elevated ORs, we observed no statistically significant association (data not shown).

Discussion

In this population-based case–control study, self-reported diabetes was associated with an increased risk of pancreatic and liver cancers. However, the elevated risk of pancreatic cancer was completely restricted to those whose diabetes was diagnosed in the year preceding cancer diagnosis, suggesting that diabetes was a consequence rather than a cause. For other cancer types investigated, there was no apparent increase in risk among diabetics. Because of the relatively small size of some cancer case groups, weak or even moderate associations with diabetes cannot be entirely ruled out.

Methodological issues

The main methodological issues to consider in studying an association between diabetes and cancer in a case–control study are detection bias, reverse causality, confounding and misclassification of diabetes status.

Detection bias could result in an apparent excess of cancer among diabetics if they received a more thorough medical follow-up than the general population. In our study, as in others, detection bias cannot be entirely ruled out. Closer medical follow-up of diabetics could have led to an increased detection of all cancers of the gastrointestinal (GI) tract, given the frequency of GI complications among diabetics. However, the most common GI tumors were not more frequent among diabetics in our study, suggesting that the observed associations were not due to detection bias.

Reverse causality is a plausible explanation, especially for an association with pancreatic cancer. Pancreatic tumors can result in impaired glucose metabolism by inducing insulin resistance.[30] Thus, diabetes with onset shortly before the diagnosis of pancreatic cancer may well reflect reverse causality. We addressed this issue by stratifying for the length of the interval between the diagnoses of diabetes and cancer.

TABLE I – SELECTED CHARACTERISTICS AMONG POPULATION CONTROLS AND CANCER CASES

Cancer type	*N*	Age (years)[1]	Income (1981 CAN$)[1]	Ethnicity (% French)	Ever smoked (%)	BMI % ≥ 25 kg/m^2
Population controls	509	59.6 ± 7.9	26,511 ± 8,691	64.0	80.2	58.2
Esophagus	90	59.8 ± 7.6	24,271 ± 8,010	64.4	93.3	44.5
Stomach	226	58.3 ± 8.2	24,250 ± 8,332	58.8	88.5	42.5
Colon	435	59.4 ± 7.6	25,941 ± 8,797	54.7	80.7	54.5
Rectum	234	58.6 ± 8.0	26,264 ± 9,183	58.5	79.9	53.4
Liver	34	59.9 ± 8.6	23,096 ± 8,456	61.8	79.4	58.8
Pancreas	92	58.8 ± 7.6	25,791 ± 9,811	58.7	87.0	54.4
Lung	752	59.2 ± 7.0	22,424 ± 7,961	69.0	98.4	45.4
Prostate	394	62.9 ± 5.0	24,800 ± 9,030	65.0	82.7	57.8
Bladder	437	59.1 ± 7.6	25,828 ± 10,038	58.1	91.8	49.0
Kidney	158	58.2 ± 7.6	26,298 ± 9,042	53.8	80.4	59.5
Melanoma	94	52.9 ± 10.1	29,650 ± 8,896	36.2	64.9	57.4
Non-Hodgkin's lymphoma	195	55.1 ± 9.6	26,256 ± 8,296	63.1	82.6	55.4

[1]Values indicate mean ± SD.

TABLE II – PROPORTION OF DIABETICS BASED ON TWO DEFINITIONS AMONG POPULATION CONTROLS AND CANCER CASES

Cancer type	*N*	Definition of diabetes		Median time since diagnosis of diabetes (years)
		Self-reported diabetes n_1 (%)	Self-reported diabetes and medication use n_2 (%)[1]	
Population controls	509	42 (8.3)	32 (6.3)	5.0
Esophagus	90	9 (10.0)	7 (7.8)	10.0
Stomach	226	15 (6.6)	11 (4.9)	5.0
Colon	435	41 (9.4)	27 (6.2)	8.0
Rectum	234	16 (6.8)	10 (4.3)	4.5
Liver	34	8 (23.5)	6 (17.6)	5.0
Pancreas	92	15 (16.3)	13 (14.1)	1.0
Lung[2]	752	47 (6.3)	34 (4.5)	9.5
Prostate	394	46 (11.7)	36 (9.1)	8.0
Bladder[2]	437	36 (8.2)	22 (5.0)	11.0
Kidney[2]	158	16 (10.1)	12 (7.6)	6.5
Melanoma	94	4 (4.3)	1 (1.1)	5.0
Non-Hodgkin's lymphoma[2]	195	16 (8.2)	10 (5.1)	7.0

[1]n_2 is a proper subset of n_1. That is, this definition comprises those who reported that they had been diagnosed as diabetic and had used medication for it.–[2]Two subjects with lung cancer, 2 with bladder cancer, 1 with kidney cancer and 2 with Non-Hodgkin's lymphoma were diagnosed with diabetes before age 30.

TABLE III – ODDS RATIOS FOR THE ASSOCIATION BETWEEN DIABETES AND CANCER, USING TWO DEFINITIONS OF DIABETES

Cancer type	Subjects without diabetes (*no*)	Definition of diabetes			
		Self-reported diabetes		Self-reported diabetes and medication use	
		n_1	OR[1] (95% CI)	n_2	OR[1] (95% CI)
Population controls	467	42	1.0	32	1.0
Esophagus[2,3,4,5,6]	81	9	1.3 (0.6, 3.1)	7	1.4 (0.5, 3.6)
Stomach[2,3,4]	211	15	1.0 (0.5, 1.8)	11	0.9 (0.4, 1.9)
Colon[2,3,4]	394	41	1.2 (0.7, 1.8)	27	1.0 (0.6, 1.7)
Rectum[2,4]	218	16	0.9 (0.5, 1.6)	10	0.8 (0.4, 1.6)
Liver[2,4,10]	26	8	3.1 (1.1, 8.8)	6	4.3 (1.4, 13.3)
Pancreas[2,3,4,5]	77	15	2.1 (1.0, 4.3)	13	2.6 (1.1, 5.7)
Lung[2,3,7]	705	47	0.8 (0.5, 1.3)	34	0.7 (0.4, 1.2)
Prostate[2,4,9]	348	46	1.2 (0.7, 1.9)	36	1.2 (0.7, 2.0)
Bladder[2,3,5,8]	401	36	1.0 (0.6, 1.7)	22	0.8 (0.4, 1.5)
Kidney[2,4,5]	142	16	1.3 (0.7, 2.4)	12	1.3 (0.6, 2.7)
Melanoma[3]	90	4	0.6 (0.2, 1.9)	1	0.2 (0.03, 1.9)
Non-Hodgkin's lymphoma[9]	179	16	1.3 (0.7, 2.4)	10	1.1 (0.5, 2.4)

[1]All models were adjusted for age, family income, years of schooling, ethnicity, proxy status, body mass index. Additional adjustments for.–[2]Tobacco smoking.–[3]β-carotene consumption.–[4]Alcohol consumption.–[5]Coffee consumption.–[6]Tea consumption.–[7]Occupational exposure to asbestos and silica.–[8]Occupational exposure to aromatic amines.–[9]Farming.–[10]History of hepatitis.

TABLE IV – ADJUSTED ODDS RATIOS FOR THE ASSOCIATION BETWEEN DIABETES AND CANCER RISK, STRATIFIED ACCORDING TO THE TIME INTERVAL BETWEEN THE DIAGNOSES OF DIABETES AND CANCER[1]

Diabetes status	Population controls *n*	Pancreatic cancer[2]		Liver cancer[3]	
		n	OR (95% CI)	*n*	OR (95% CI)
No diabetes	467	77	1.0	26	1.0
Diabetes					
≤1 year	6	8	10.5 (2.9, 38.7)	0	–
>1 to <5 years	17	2	1.3 (0.2, 6.8)	2	4.2 (0.7, 24.7)
≥5 years	19	5	1.1 (0.4, 3.3)	6	3.4 (1.0, 12.0)

[1]All models were adjusted for age, family income, years of schooling, ethnicity, proxy status and BMI.–[2]Further adjusted for tobacco smoking, β-carotene, alcohol and coffee consumption.–[3]Further adjusted for tobacco smoking, alcohol consumption and history of hepatitis.

Confounding by obesity, particularly for kidney cancer, and by alcohol consumption for liver and pancreatic cancers was suggested as a possible source of bias in earlier studies.[31] We were able to account for these potentially important confounders.

Diabetes status was based on self-report. The validity of self-report for diabetes has been documented for several populations,[32–36] suggesting good to very good agreement between self-report and medical records. However, some misclassification is bound to occur given the proportion of undiagnosed diabetics.[1] If nondifferential between cases and controls, this misclassification would result in a bias toward the null; if differential, the estimates could be biased away or toward the null value. We compared the

median number of medical conditions reported in a checklist of 10 conditions (*e.g.*, tuberculosis, stomach or duodenal ulcers, asthma, high blood pressure, rheumatism/arthritis, etc.) between cases and controls. Cancer cases did not report more medical conditions, suggesting that self-report of diabetes was not systematically more likely among cases than controls, and that misclassification of diabetes status was likely nondifferential.

Advantages and limitations of our study

Our study offered important advantages to assess a link between diabetes and several cancer types. A common methodology was used for all cancers, information on potential confounders (nonoccupational and occupational) was available, and cases consisted of histologically-confirmed primary incident cancers. The information we elicited on history of diabetes included the age at diagnosis and whether medication was used. The main limitations were the relatively small numbers for some cancer types that did not allow the ruling out of weak or moderate associations with diabetes, and the self-reported nature of diabetes.

Interpretation of results

For 10 types of cancer, we found no meaningful associations with history of diabetes. We observed an association between diabetes and pancreatic cancer, which was confined to the recent onset of diabetes. Several investigators have reported that the magnitude of the association between diabetes and pancreatic cancer decreased with a longer duration of diabetes, in some cases disappearing or becoming non statistically significant.[15–18] However, in other reports, the excess risk of pancreatic cancer persisted even among those with a longer duration of diabetes, suggesting that diabetes may have preceded cancer onset.[19,21,22,37] Our observations strengthen the evidence from the former group of studies, and strongly suggest that diabetes is an early manifestation of pancreatic cancer rather than a cause. Results from a meta-analysis of 36 studies on type 2 diabetes and pancreatic cancer suggest that there is indeed evidence of reverse causality, but also support the presence of a modest causal association between diabetes and pancreatic cancer.[38]

By contrast, an increased risk of liver cancer among diabetics was apparent both among individuals with short and long intervals between diabetes and cancer diagnoses, thereby strengthening the evidence that diabetes may play an etiological role. A possible link between diabetes and liver cancer has been investigated in several studies. While earlier studies did not suggest an association,[14,15] more recent ones point to diabetes as a risk factor for liver cancer.[18,20,21,26,37,39–42] Our results are in agreement with these latter studies. There are specific difficulties inherent to teasing out the causal sequence between diabetes and liver cancer. Chronic liver disease can result in glucose tolerance and, to a lesser degree, diabetes.[41] But diabetes is in turn a risk factor for nonalcoholic liver disease, which can lead to cirrhosis, and eventually to hepatocellular carcinoma (HCC). The temporal sequence was further documented in a large prospective U.S. study in which the occurrence of diabetes preceded both chronic liver disease and HCC. Moreover, diabetes was associated with both conditions independent of other factors such as alcoholic liver disease and viral hepatitis.[41]

The biological mechanism behind an effect of diabetes on liver cancer remains hypothetical. Individuals with type 2 diabetes often present insulin resistance, compensatory hyperinsulinemia and elevated levels of IGF-1,[43] which may result in enhanced hepatic cell proliferation.[20] There are indications that higher blood glucose levels are associated with mortality due to liver and other cancers.[37,44] Biomarker studies focusing on insulin, IGF family molecules and blood glucose levels are needed to elucidate the biological mechanism linking diabetes to carcinogenesis.

In conclusion, we observed an association between diabetes mellitus and subsequent risk of liver cancer among men. According to our results, the ostensible association between diabetes and pancreatic cancer is an artifact due to reverse causality. For other cancer types investigated, there was no apparent excess risk among diabetics.

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