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Note

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Cancer Incidence in a Population-Based Cohort of Patients Hospitalized With Diabetes Mellitus in Denmark

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Background: **Diabetes has been associated with an increased risk of several cancers, notably cancers of the pancreas, liver, endometrium, and kidney. Since most previous studies have involved a limited sample size or focused on specific cancer sites, we conducted a comprehensive assessment of the risk of cancer in a nationwide cohort of diabetics in Denmark.** ***Methods:*** **Discharge records of 109 581 individuals hospitalized with a diagnosis of diabetes from 1977 through 1989 were linked with national cancer registry records through 1993. Standardized incidence ratios (SIRs) were calculated for specific cancer sites.** ***Results:*** **The SIRs for primary liver cancer were 4.0 (95% confidence interval [CI] = 3.5–4.6) in males and 2.1 (95% CI = 1.6–2.7) in females. These SIRs remained elevated with increasing years of follow-up and after exclusion of patients with reported risk factors (e.g., cirrhosis and hepatitis) or patients whose cancers were diagnosed at autopsy. Kidney cancer risk was also elevated, with SIRs of 1.4 (95% CI = 1.2–1.6) in males and 1.7 (95% CI = 1.4–1.9) in females. For both sexes combined, the SIR for pancreatic cancer was 2.1 (95% CI = 1.9–2.4), with a follow-up time of 1–4 years; this SIR declined to 1.3 (95% CI = 1.1–1.6) after 5–9 years of follow-up. Excess risks were also observed for biliary tract and endometrial cancers. The SIRs for kidney and endometrial cancers declined somewhat after exclusion of diabetics with reported obesity.** ***Conclusions:*** **Patients hospitalized with a diagnosis of diabetes appear to be at higher risk of developing cancers of the liver, biliary tract, pancreas, endometrium, and kidney. The elevated risks of endometrial and kidney cancers, however, may be confounded by obesity. [J Natl Cancer Inst 1997;89:1360–5]**

Diabetes mellitus is a metabolic disease of two major subtypes that is characterized by abnormalities in the synthesis and cellular uptake of insulin, a critical hormonal regulator of glucose metabolism. In insulin-dependent diabetes mellitus (IDDM), insulin synthesis ceases as a result of the autoimmune destruction of insulin-producing pancreatic islet cells, which is thought to be triggered by an environmental factor (i.e., viral infection) primarily in individuals who are positive for the histocompatibility antigens HLA-DR3 and/or HLA-DR4 *(1)*. In noninsulin dependent diabetes mellitus (NIDDM), pancreatic islet cells continue to secrete insulin, but target tissues (e.g., muscle and liver) are resistant to its uptake and use because of a decrease in the number of insulin receptors, alterations in postreceptor function, or the presence of blocking antibodies.

Elevated risks have been reported in diabetics for several cancers, notably cancers of the pancreas *(2,3)*, liver *(4–8)*, endometrium *(5,8)*, and kidney *(5,9)*. Most previous studies of cancer risk in diabetics have been based on a limited sample size, or they have focused on population subgroups or specific cancer sites. This study provides a comprehensive assessment of multiple cancer sites in a large, population-based cohort of diabetics and was undertaken by linking computerized records from nationwide hospital and cancer registries in Denmark.

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See ''Notes'' following ''References.''

Methods

The cohort was established by identifying all males and females in the Danish Central Hospital Discharge Register who were hospitalized with diabetes as a primary or a secondary diagnosis during the years 1977 through 1989. From 1977 through 1986, these individuals were identified by International Classification of Diseases [ICD]-8 code 250 for diabetes *(10),* and, from 1987 through 1989, by revised codes from the Danish National Board of Health that distinguished IDDM and NIDDM. The cohort entry date was defined as the first day of the month after the initial hospital discharge in which diabetes was identified.

Of the 117 689 diabetics initially identified, 8106 were excluded from the cohort because they died during the brief interval between hospital admission and the cohort entry date, while an additional two individuals were excluded because of questionable age data, leaving a total of 109 581 diabetics for inclusion in the cohort. Estimates of cancer risk in the cohort exclude the 2222 cancers (and corresponding 97 267 person-years) diagnosed during the first year of follow-up, which were assumed to be prevalent at cohort entry and possibly diagnosed as a result of clinical evaluation for diabetes. However, the subjects with these 2222 cancers were retained in the analysis because they remained at risk of developing another primary cancer and national incidence rates in Denmark include multiple primaries.

To ascertain cancer incidence in the cohort, computerized hospital discharge records were linked to the Danish Cancer Registry by use of a personal identification number assigned to all Danish citizens. The total number of incident cancers observed during the follow-up period was 11 053. The cohort exit date was defined as either the date of death or December 31, 1993. Additional information was obtained from the Hospital Discharge Register on up to 20 medical conditions reported at each admission during the observation period. The Hospital Discharge Register *(11)* and the Cancer Registry *(12)* have reported a completeness of registration of more than 97% for discharges and incidence of cervical cancer.

Site-specific standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated to compare the observed number of incident cancers with the expected. The number of expected cancers was generated by multiplying the number of person-years in the cohort by the national cancer incidence rates, specified for sex and 5-year-age and calendar year categories. For individuals with multiple primary tumors (including second primaries of the same site), each tumor was counted separately in the analysis. Site-specific SIRs were also stratified on the basis of sex, length of follow-up in years, diabetes type for those entering the cohort from 1987 through 1989, and whether or not the hospital records mentioned obesity, a confounding risk factor for several cancers. Chi-squared tests *(13)* were used to assess trends in risk estimates according to years of follow-up. Primary liver cancer SIRs were further stratified on the basis of the presence or absence of cancer-associated medical conditions, and, along with renal cell cancer, according to the inclusion or exclusion of autopsy-diagnosed cases from both the observed and the expected numbers.

To address concerns of selection bias arising from the use of a hospitalized study population, SIRs were stratified on the basis of diabetes diagnostic order (i.e., whether diabetes was the sole or the primary hospital discharge diagnosis at cohort entry or whether it was a secondary diagnosis). Presumably, SIRs would be higher in the stratum with diabetes as a secondary diagnosis if subjects were preferentially selected into the cohort by virtue of having other hospital diagnoses that predisposed to subsequent cancer.

Results

After exclusion of ineligible subjects and of cancers diagnosed within 1 year of cohort entry, a total of 8831 incident cancers and 628 129 person-years were included in the present analyses. Among the 19 363 cohort members accrued from 1987 through 1989 (17.7% of the total cohort), when diabetes subtypes could be differentiated by diagnostic codes, 15 495 (80%) were assigned a code for NIDDM and 3868 (20%) were assigned a code for IDDM. The overall median age at cohort entry was 64 years in males (n = 54 571) and 69 years in females (n = 55 010), with 4.3% of the cohort entering prior to the age of 20 years. The median age for patients with NIDDM entering the cohort from 1987 through 1989 was 69 years compared with 51 years for patients with IDDM. A total of 56.3% of the cohort died during follow-up.

Sex-specific SIRs for major cancer sites are shown in Table 1. Elevated risks of digestive system cancers were observed in both males and females. These higher risks were primarily due to excess liver, pancreatic, and biliary tract tumors. Most notably, the SIR of primary liver cancer was 4.0 (95% CI = 3.5–4.6) in males and 2.1 (95% CI = 1.6–2.7) in females. Approximately 60% of these liver cancers were hepatocellular carcinoma, 19% were cholangiocarcinoma, and 2.5% were combined hepatocellular and cholangiocarcinoma, while the remainder were primarily miscellaneous rare types (1.5%), unspecified tumors (10%), or tumors that were not histologically confirmed (7%). The histologic distribution of primary liver cancers among diabetics and the percentage of histologically confirmed tumors approximated that of the tumor registry.

Table 1. Standardized incidence ratios (SIRs) of cancer in patients hospitalized with diabetes at cohort entry, stratified according to sex (Denmark, 1977–1989)

Type of cancer (ICD-7 code[s])*	Males			Females		
	No.	SIR	95% CI†	No.	SIR	95% CI
All cancers (140–205)	4666	1.1	1.1–1.1	4165	1.1	1.1–1.1
Mouth and pharynx (140–148)	118	1.2	1.0–1.4	54	1.2	0.9–1.6
Digestive organs (150–159)	1433	1.4	1.3–1.5	1206	1.2	1.2–1.3
Esophagus (150)	67	1.3	1.0–1.6	26	1.0	0.7–1.5
Stomach (151)	188	1.2	1.0–1.3	131	1.1	1.0–1.4
Small intestine (152)	14	1.3	0.7–2.2	12	1.3	0.7–2.2
Colon (153)	413	1.3	1.1–1.4	442	1.1	1.0–1.2
Rectum (154)	235	1.1	0.9–1.2	167	1.0	0.9–1.2
Liver (155.0)	190	4.0	3.5–4.6	68	2.1	1.6–2.7
Biliary tract (155.1–.3)	39	1.4	1.0–1.9	81	1.4	1.1–1.8
Pancreas (157)	206	1.7	1.5–2.0	211	1.6	1.4–1.9
Larynx (161)	61	1.0	0.8–1.3	5	0.5	0.2–1.1
Lung (162)	713	1.0	0.9–1.1	250	0.9	0.8–1.1
Breast (170)	7	1.1	0.4–2.2	777	1.1	1.1–1.2
Ovary (175)	—	—	—	129	0.9	0.7–1.0
Corpus uteri (172)	—	—	—	231	1.4	1.2–1.6
Cervix (171)	—	—	—	92	0.9	0.7–1.1
Other female genital (176)	—	—	—	61	1.5	1.2–2.0
Prostate (177)	505	0.9	0.8–1.0	—	—	—
Testis (178)	23	1.0	0.6–1.5	—	—	—
Kidney (180)	168	1.4	1.2–1.6	154	1.7	1.4–1.9
Bladder (181)	383	1.0	0.9–1.1	110	0.9	0.8–1.1
Melanoma (190)	61	1.0	0.7–1.2	77	1.0	0.8–1.3
Nonmelanoma skin (191)	613	1.0	0.9–1.1	461	0.9	0.8–0.9
Brain, nervous system (193)	80	1.1	0.9–1.4	79	1.1	0.8–1.3
Thyroid (194)	10	1.3	0.6–2.3	21	1.2	0.7–1.8
Endocrine (195)	5	1.4	0.5–3.4	0	0.0	0.0–1.4
Lymphatic and hematopoietic (200–205)	272	1.1	1.0–1.2	239	1.1	1.0–1.3
Lymphoma (200–202)	108	1.1	0.9–1.3	97	1.1	0.9–1.4
Multiple myeloma (203)	48	1.0	0.8–1.4	52	1.3	1.0–1.7
Leukemia (204)	116	1.1	0.9–1.3	90	1.1	0.9–1.4

*ICD-7 = International Classification of Diseases, seventh revision *(43)*.

†95% CI = 95% confidence interval.

The SIR for pancreatic cancer in males (1.7; 95% CI = 1.5–2.0) was similar to the SIR in females (1.6; 95% CI = 1.4–1.9). SIRs for biliary tract cancers were 1.4 (95% CI = 1.0–1.9) in males and 1.4 (95% CI = 1.1–1.8) in females. A modest elevation was observed for colon cancer in males (SIR = 1.3; 95% CI = 1.1–1.4). Kidney cancer risk was elevated in both males (SIR = 1.4; 95% CI = 1.2–1.6) and females (SIR = 1.7; 95% CI = 1.4–1.9). Endometrial cancer was also found to occur in excess (SIR = 1.4; 95% CI = 1.2–1.6). Diabetics with reported obesity, who constituted 12% of the cohort, had somewhat higher SIRs for kidney (2.0; 95% CI = 1.5–2.6) and endometrial (2.0; 95% CI = 1.6–2.6) cancers than those without reported obesity (1.4; 95% CI = 1.3–1.6 and 1.2; 95% CI = 1.1–1.4, respectively). The SIR of breast cancer in females was 1.1 (95% CI = 1.1–1.2).

Given the broadly similar risk patterns among males and females, the observed numbers of cancers were pooled, and SIRs were calculated stratifying on the basis of age group at cohort entry (<50 years versus 50 years or more). In view of the age differences for patients with NIDDM versus IDDM entering the cohort from 1987 through 1989, SIRs in the 50 years or more stratum were assumed to reflect cancer risk in a population with predominantly NIDDM, while SIRs in the less than 50 years stratum were assumed to represent cancer risk in a heterogeneous population with a comparatively high percentage of patients with IDDM. To further assess possible differences, SIRs were calculated according to diabetes subtype in the subset entering the cohort from 1987 through 1989.

Primary liver cancer was elevated nearly fivefold in the less than 50 years age-at-entry stratum and threefold in the 50 years or more stratum (Table 2). Pancreatic and kidney cancers were also elevated in both strata, although the 95% CI in the less than 50 years stratum included 1.0 (Table 2). Significant elevations of 40%–50% were observed for biliary tract, endometrial, and vulvar/vaginal (e.g., other female genital) cancers in the 50 years or more stratum, whereas cancers of the mouth and pharynx and of the esophagus were elevated twofold to threefold in the less than 50 years stratum (Table 2).

On the basis of small numbers in the subset entering the cohort from 1987 through 1989, SIRs were suggestive of an elevated risk of liver, biliary tract, and pancreatic cancers in patients with either IDDM or NIDDM. In patients with IDDM, the SIRs were 2.9 (95% CI = 0.6–8.4) for liver, 4.2 (95% CI = 1.1–10.9) for biliary tract, and 3.5 (95% CI = 1.8–6.3) for pancreatic cancers. In patients with NIDDM, the SIRs were 3.1 (95% CI = 2.0–4.7) for liver, 1.8 (95% CI = 0.9–1.3) for biliary tract, and 1.7 (95% CI = 1.2–2.3) for pancreatic cancers. A marginal excess of cancers of the mouth and pharynx (SIR = 1.5; 95% CI = 0.9–2.3) was also observed in patients with NIDDM.

Since hospitalization for diabetes or diabetes-related conditions may have increased the likelihood of detecting prevalent cancers, SIRs were stratified on the number of follow-up years from cohort entry to cancer diagnosis. Liver cancer showed no trend of increasing or decreasing risk with the length of follow-up for either sex alone (Table 3) or both sexes combined. In contrast, pancreatic cancer SIRs decreased from 2.1 (95% CI = 1.9–2.4) for a follow-up time of 1–4 years to 1.3 (95% CI = 1.1–1.6) for a follow-up time of 5–9 years and 1.3 (95% CI = 0.9–1.7) for a follow-up time of 10 years or more (two-sided test for trend; $P<.0001$). The other cancer sites examined showed no significant variation in risk with increasing time interval between cohort entry and cancer diagnosis.

The potentially confounding effects of coexisting medical conditions associated with liver cancer were assessed by stratifying SIRs on the presence or absence of the following diagnoses in hospital records: hepatitis, cirrhosis and other liver disorders (ICD-8 codes 070 and 570–573); alcohol dependence and other alcohol-related conditions (ICD-8 codes 291, 303, 577.1, and 980); cholelithiasis and other disorders of the gallbladder and biliary tract (ICD-8 codes 574–576); jaundice (ICD-8 codes 283 and 785); obesity (ICD-8 code 277); and hemochromatosis (ICD-8 codes 273.2 and 279). Liver cancer SIRs were nearly four times higher in

Table 2. Standardized incidence ratios (SIRs) of cancer in patients hospitalized with diabetes at cohort entry, stratified according to age at entry (Denmark, 1977–1989)

Type of cancer (ICD-7 code[s])*	<50 years			50 years or more		
	No.	SIR	95% CI†	No.	SIR	95% CI
All cancers (140–205)	660	1.1	1.0–1.2	8171	1.1	1.1–1.1
Mouth and pharynx (140–148)	30	1.8	1.2–2.6	142	1.1	0.9–1.3
Digestive organs (150–159)	135	1.7	1.4–2.0	2504	1.3	1.2–1.4
Esophagus (150)	17	3.3	1.9–5.3	76	1.0	0.8–1.3
Stomach (151)	16	1.4	0.8–2.3	303	1.1	1.0–1.3
Small intestine (152)	0	—	—	26	1.4	0.9–2.0
Colon (153)	36	1.3	0.9–1.8	819	1.2	1.1–1.2
Rectum (154)	21	1.2	0.8–1.9	381	1.0	0.9–1.1
Liver (155.0)	17	4.8	2.8–7.7	241	3.2	2.8–3.6
Biliary tract (155.1–.3)	3	1.2	0.2–3.5	117	1.4	1.2–1.7
Pancreas (157)	13	1.4	0.7–2.3	404	1.7	1.5–1.9
Larynx (161)	12	1.6	0.8–2.8	54	0.9	0.6–1.1
Lung (162)	78	1.3	1.0–1.6	885	0.9	0.9–1.0
Breast (170)	87	0.9	0.7–1.1	697	1.2	1.1–1.2
Ovary (175)	15	1.0	0.6–1.6	114	0.8	0.7–1.0
Corpus Uteri (172)	8	0.7	0.3–1.4	223	1.4	1.2–1.6
Cervix (171)	24	1.0	0.7–1.5	68	0.8	0.7–1.1
Other female genital (176)	4	2.5	0.7–6.3	57	1.5	1.1–2.0
Prostate (177)	7	1.0	0.4–2.1	498	0.9	0.8–1.0
Testis (178)	11	0.6	0.3–1.1	12	1.8	1.0–3.2
Kidney (180)	21	1.6	1.0–2.4	301	1.5	1.3–1.7
Bladder (181)	22	0.9	0.6–1.4	471	1.0	0.9–1.1
Melanoma (190)	20	0.7	0.4–1.1	118	1.1	0.9–1.3
Nonmelanoma skin (191)	71	0.8	0.6–1.0	1003	0.9	0.9–1.0
Brain, nervous system (193)	35	1.3	0.9–1.8	124	1.0	0.9–1.2
Thyroid (194)	2	0.5	0.1–1.8	29	1.4	0.9–1.9
Endocrine (195)	1	1.2	0.02–6.9	4	0.8	0.2–2.0
Lymphatic and hematopoietic (200–205)	38	1.0	0.7–1.4	473	1.1	1.0–1.2
Lymphoma (200–202)	16	1.0	0.6–1.6	183	1.1	1.0–1.3
Multiple myeloma (203)	6	1.5	0.5–3.2	93	1.2	0.9–1.4
Leukemia (204)	10	0.8	0.4–1.5	196	1.1	1.0–1.3

*ICD-7 = International Classification of Diseases, seventh revision *(43)*.
†95% CI = 95% confidence interval.

Table 3. Sex-specific standardized incidence ratios (SIRs) of liver cancer, stratified according to years of follow-up, presence of associated diseases, and autopsy diagnosis

Variable	Males			Females		
	No.	SIR	95% CI*	No.	SIR	95% CI
Years of follow-up†						
1–4	90	4.4	3.5–5.4	32	2.3	1.6–3.2
5–9	69	3.6	2.8–4.6	24	1.8	1.2–2.7
⩾10	31	4.2	2.8–5.9	12	2.4	1.2–4.1
Reported presence of associated diseases‡						
No	97	2.6	2.1–3.1	35	1.4	1.0–2.0
Yes	93	9.9	8.0–12.1	34	2.4	1.7–3.4
Incidental diagnosis of liver cancer at autopsy						
Included	190	4.0	3.5–4.6	68	2.1	1.6–2.7
Excluded	132	3.5	3.0–4.2	45	1.6	1.1–2.1

*95% CI = 95% confidence interval.

†Excludes cancers diagnosed less than 1 year after cohort entry.

‡Includes hepatitis, cirrhosis, and other liver disorders, alcohol dependence and other alcohol-related conditions, cholelithiasis and other disorders of the gallbladder and biliary tract, jaundice, obesity, and hemochromatosis.

males and nearly twice as high in females with a co-diagnosis of any of the above conditions compared with SIRs in subjects without any such diagnosis (Table 3), although an elevation in risk was still evident in the latter group.

Autopsy diagnoses of cancer were considered a potential source of detection bias, since diabetics may have higher autopsy rates than the underlying population and, thus, a greater likelihood of incidental cancers reported at death. Therefore, SIRs for primary liver and renal cell cancers, which both have a relatively high frequency of incidental autopsy diagnosis, were re-calculated excluding incidental autopsy-diagnosed cancers from the numerator and from the rates used to generate expected numbers in the denominator. These ratios were compared to SIRs that included autopsy-diagnosed cancers. Sixty-nine percent of male and 66.1% of female cases of primary liver cancer remained in the numerator after exclusion of incidental autopsy-diagnosed cases. The resulting SIRs were slightly lower, although essentially similar to the original ratios (Table 3). A total of 71.4% of renal cell cancers in males and 65.4% in females remained after exclusion of the incidental autopsy-diagnosed cases. However, the SIRs were again very similar. In males, the SIR excluding the autopsy-diagnosed cases was 1.3 (95% CI = 0.9–1.7) compared with a SIR of 1.4 (95% CI = 1.2–1.6) for all renal cell cancers, while in females, the respective SIRs were 1.8 (95% CI = 1.3–2.3) and 1.7 (95% CI = 1.4–1.9).

Diabetes was listed as the sole hospital discharge diagnosis for 25 291 (23.1%) subjects at cohort entry, as the primary but not sole diagnosis for 25 390 (23.2%) subjects, and as a secondary diagnosis for 58 900 (53.7%) subjects. The SIRs of liver and pancreatic cancers were the same in subjects with diabetes as the sole or primary diagnosis and in subjects with diabetes as a secondary diagnosis. SIRs were slightly higher in the secondary diagnosis group for both kidney (1.6; 95% CI = 1.4–1.8 versus 1.4; 95% CI = 1.1–1.6) and endometrial (1.5; 95% CI = 1.3–1.8 versus 1.2; 95% CI = 1.0–1.5) cancers. Circulatory disease constituted 39% of the primary diagnoses in subjects with diabetes as a secondary diagnosis.

A total of 4.8% of subjects were diagnosed with more than one primary cancer during the follow-up period. Unusual clusters of diabetes-associated multiple primaries within subjects were not observed. Among subjects with primary liver cancer, 7.4% had another primary tumor, the most common of which were lung, colorectal, and breast cancers. Among those with kidney cancer, 13% were diagnosed with another primary tumor, one quarter of which were bladder cancers.

Discussion

The main findings in this study indicate that there is an elevated incidence of cancers of the liver, biliary tract, pancreas, kidney, and endometrium in patients hospitalized with a reported diagnosis of diabetes. With the exception of liver cancer, the magnitude of the SIRs for these cancers was small, suggesting that diabetes is unlikely to explain a substantial proportion of them. The elevated incidence of these cancers persisted with increasing years of follow-up, although the SIR of pancreatic cancer declined from 2.1 to 1.3 after 5 years. There were no striking excesses or deficits according to age at cohort entry that would suggest a relationship between the above-named cancers and diabetes subtype, although the modest excess in endometrial cancer was restricted to the 50 years or more stratum. For reasons that are not clear, although chance is possible, elevated risks of oral/pharyngeal and esophageal cancers were observed in cohort members entering prior to the age of 50 years. The preponderance of NIDDM diagnoses (80% of total) among cohort members entering from 1987 through 1989, when diagnostic codes distinguished the two diabetes subtypes, implies that these results mainly reflect cancer risk associated with NIDDM.

This study confirmed the excess of primary liver cancer reported among diabetics in several recent studies from Italy *(4),* Sweden *(5,7),* Los Angeles *(6),* and Japan *(14)* and further demonstrated that the diagnosis of diabetes preceded the diagnosis of liver cancer by many years. While the excess was highest in diabetics with reported medical conditions associated with liver cancer, SIRs were also elevated in the stratum with individuals who lacked these conditions, although the latter SIRs probably underestimate the true risk because national cancer rates applied to the denominator include individuals with these conditions. On the other hand, underreporting of alcoholism, asymptomatic hepatitis infection, and hemochromatosis in hospital records may result in overestimation of risk.

The causal mechanisms for an excess risk of liver cancer in diabetics are unclear, although alcohol consumption may be involved as a risk factor for both conditions. Alcohol consumption has been related to both liver cancer *(15)* and diabetes *(16–19),* although not all prospective studies *(20–22)* have found an association with NIDDM. Through another mechanism, the liver of diabetics and of obese persons may undergo fatty changes (steatosis), with the potential for necrosis

(steatohepatitis) and fibrotic progression to cirrhosis, perhaps resulting from the cellular accumulation of toxic free fatty acids in insulin-deficient cells *(16,23–25)*.

Although the risk of pancreatic cancer in this study decreased significantly with years of follow-up, a 30% excess remained after 5 or more years. A number of cohort and case–control studies that examined pre-existing diabetes as a risk factor for pancreatic cancer have reported equivocal results *(26)*, and a temporal sequence in which the diagnosis of diabetes precedes the diagnosis of cancer has not been uniformly established *(27,28)*. A direct causal link of diabetes to pancreatic cancer has been questioned because only a small percentage of pancreatic tumors arise in insulin-producing islet cells and most are of exocrine origin. Alternatively, it has been postulated that diabetes and pancreatic cancer are separate, histologically specific responses to a common etiologic factor *(29)*.

Several other cancers were observed to be in excess in this study, including cancers of the kidney in both sexes, of the colon in males, and of the endometrium. In view of the association between diabetes and obesity, it is noteworthy that these cancers were also elevated in a Danish record linkage study of obesity and cancer *(30)*. Obesity and, in particular, central adiposity are recognized risk factors for endometrial cancer *(31)* and postmenopausal breast cancer *(32,33)*, as well as predictors of insulin resistance and hyperinsulinemia *(34)*. Although insulin resistance has been linked to breast cancer risk in one study, independent of body mass index or distribution of adiposity *(35)*, several other studies *(5,36,37)* have not found a relationship of diabetes per se with premenopausal or postmenopausal breast cancer, in concurrence with the results of this study.

Gallbladder cancer, particularly in women, has also been associated with obesity and type of fat distribution, which may reflect a greater prevalence among the obese of carcinogenic risk factors, such as gallstones, cholesterol-supersaturated bile, or high levels of endogenous estrogens *(38)*. In this study, where the SIR of biliary tract cancer was 1.4, diabetes may be functioning as a marker of these risk factors through its association with obesity. A similar effect may explain the excess of colon cancer in male diabetics. In this study, SIRs for gallbladder and colon cancers did not differ among diabetics with and without reported obesity, although underreporting of obesity may have obscured true differences between these strata.

Several studies *(9,39–41)* have reported elevated relative risks of kidney cancer in diabetics, although these risks were not statistically significant or were of borderline significance after adjustment for obesity, a known risk factor for renal cell cancer. An association of renal dialysis with some forms of renal carcinoma and predisposing cysts has been reported *(42)*, and such dialysis may be a relevant risk factor among the subset of diabetics in this cohort who received dialysis for diabetes-related renal disease.

The linkage of national hospital and cancer registries in Denmark to examine cancer outcomes in diabetics has several important advantages. A large sample size was obtained that provided the necessary statistical power to examine site-specific cancer incidence and to analyze further the patterns of risk according to sex and other descriptive variables. The large sample size also provided the opportunity to rule out associations with common cancers such as prostate cancer, which showed no elevation in risk among diabetics. Furthermore, by excluding cancers diagnosed prior to cohort entry from the analyses, a temporal sequence was established in which the diagnosis of diabetes preceded that of cancer. Stratification on the basis of years of follow-up and exclusion of cancers diagnosed within the first year of follow-up or at autopsy demonstrated that detection biases (i.e., increased cancer diagnoses at the time of hospitalization with diabetes or at autopsy) could not fully explain the elevated risks of cancers, such as those of the pancreas, liver, and kidney.

Interpretation of the results of this study is limited by the lack of extensive, reliable data on potentially relevant covariates, including obesity and alcohol consumption, and also by the absence of specific diagnostic codes to distinguish IDDM and NIDDM for most of the time period under observation. Furthermore, because the cohort was established in a hospitalized population, the results may not be generalizable to all diabetics, such as those with asymptomatic or mild disease not requiring hospitalization. Underreporting of diabetes among hospital patients with mild disease also cannot be ruled out. Given the large number of SIRs that were generated, some associations may have appeared due to chance alone. However, chance is unlikely to explain the strong associations that appeared consistently across various subgroups here and in previous studies, such as the excess of primary liver cancer.

This cohort study confirmed the notable excess risk of primary liver cancer in diabetics. The relationship between diabetes and insulin resistance and liver cancer should be explored further in molecular epidemiologic studies where covariates and biologic mechanisms are carefully considered. As the number of years of follow-up increases in which separate ICD codes for IDDM and NIDDM are available in Denmark, future record-linkage cohort studies may prove useful for studying cancer outcomes according to diabetes subtype, bearing in mind that patients who are not dependent on exogenous insulin to sustain life may still be treated with insulin and therefore be assigned the IDDM code.

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Notes

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