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Cancer risk in patients with diabetes mellitus

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Cancer incidence was ascertained in a population-based cohort of 51,008 patients in Uppsala, Sweden, who were given a discharge diagnosis of diabetes mellitus during 1965-83. Complete follow-up through 1984 with exclusion of the first year of observation showed that the observed number of cancers in females (1,294) was eight percent higher than expected (relative risk [RR] = 1.1, 95 percent confidence interval = 1.0-1.1), whereas in males the observed number (1,123) was close to the expected (RR = 1.0, 0.9-1.1). Significantly increased risks of pancreatic (RR = 1.4, 1.2-1.7), primary liver (RR = 1.5, 1.2-1.7), and endometrial (RR = 1.5, 1.2-1.8) cancers and a lower than expected number of prostatic cancers (RR = 0.7, 0.7-0 9) were found in this cohort of diabetic patients. The excess risk of pancreatic cancer was similar in females and males and evident both during one through four years (RR = 1.7, 1.4-2.1) and five through nine years (RR = 1.3, 0.9-1.7) of follow-up, but not thereafter. A similar pattern was found for primary liver cancer, but the RRs were generally higher in males than in females.

Key words: Cancer risk, cohort study, diabetes, Sweden.

Introduction

Diabetes mellitus (DM) has been associated with an increased risk of cancers of the pancreas,[1-8] liver,[9] and endometrium.[5,10,11] The hypothesis that diabetes increases the risk of pancreatic cancer has been examined previously,[1-8,12-16] but it is still uncertain whether diabetes is, in fact, an early manifestation of the malignant disease rather than a cause of it.[3-5,12] Only a few studies have had the statistical power to analyze the temporal relation between the onset of diabetes and the subsequent diagnosis of pancreatic cancer in detail; some of them were case-control studies, in which there is a potential for differences in recall between patients and controls.[6,8]

Our aim was to study cancer risk in a population-based cohort of over 50,000 patients diagnosed with DM who were followed-up to 20 years for the occurrence of cancer. Reliable data in this area are of interest both to the doctors who treat patients with DM, and to cancer epidemiologists who try to identify risk factors for cancer. Association between DM and cancer may result from shared dietary[17] or other risk factors or, alternatively, because the immunologic,[18] metabolic,[19] or hormone[20] abnormalities characteristic of the diabetic state may promote the development of cancer in susceptible individuals.

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Materials and methods

The cohort

The six-county Uppsala Health Care Region is located in central Sweden and had, during the study period, a total population of 1.2-1.3 million people. Because there is almost no private inpatient treatment in Sweden, hospital-provided medical services are, in effect, population-based and referable to the county in which the patient lives. From 1965 through 1983, the Swedish National Board of Health and Welfare received annual reports from all inpatient medical institutions in Sweden and recorded data on individual hospital admissions and discharges in the Inpatient Register. Beside national registration number—a unique personal identifier assigned to all Swedish citizens—each record contains data on place of residence, hospital department, surgical procedures, and up to eight discharge diagnoses. These diagnoses were coded according to the seventh revision of the International Classification of Diseases through 1968, and according to the eighth revision thereafter. A recent publication estimated that the extent of underreporting to the Inpatient Register was less than two percent overall.[21] Severe underreporting occurred in certain Uppsala counties during a limited period representing a few percent of the estimated total number of hospital admissions.[21]

All records in the Inpatient Register containing a diagnostic code for DM were considered for inclusion in the study. The national registration number allowed us to select the first recorded discharge with this diagnosis for each individual. The series contains a mixture of incident and prevalent cases.

A total of 56,392 individuals—30,846 females and 25,546 males—had been given a discharge diagnosis of DM at least once during 1965-83 and thus were potentially eligible. We excluded 4,272 (7.5 percent) of these individuals because they were entered in the Register with an incomplete or inconsistent national registration number and thus not available for follow-up. Another 1,112 (2.0 percent) patients were excluded due to invalid codings or to inconsistencies revealed during the record-linkages (see below). Thus, a total of 51,008 patients constituted the cohort. Their distribution by gender and age at start of follow-up is shown in Table 1, along with the number of person-years (PY) of observation.

Follow-up

Record-linkage, based on the national registration number, to the nationwide Registry of Causes of Death led to information on the date of death among those deceased through 1984. The National Swedish Cancer Registry, founded in 1958, was used to ascertain all incident cancers diagnosed in the cohort from start of follow-up until the end of 1984.[22] The time of observation was calculated from the registration date of the first diagnosis of DM until the occurrence of a cancer diagnosis, death, or the end of the observation period (31 December 1984).

The expected number of cancers was calculated by multiplying the number of PYs for each gender by age-specific cancer incidence rates for each five-year age-group and calendar year of observation. These expected rates were derived from the study population, *i.e.* the Uppsala health care region. For the main analyses, we used a one-year latency period between first registration and calculation of observed and expected numbers of cancers. The aim of this approach —applied in similar studies previously[3,5,8,12]—was to eliminate or reduce the possible impact of selection bias. Such bias occurs in patients whose cancer symptoms give rise to the hospitalization, but in whom a prevalent or newly detected diabetes is added as a discharge diagnosis.

Confounding by indication for hospitalization may arise if diseases other than diabetes were the main reason for inpatient care, provided that these diseases are associated with the occurrence of any cancer. To evaluate this possibility, we made separate calculations after a restriction of the cohort to patients with DM as the primary discharge diagnosis and as the only discharge diagnosis, respectively, on the hospital record used for cohort entry.

Statistical methods

The relative risk (RR) was defined as the ratio of observed numbers of cancers to those expected. The 95 percent confidence interval (CI) of the RR was then calculated on the assumption that the observed number follows a Poisson distribution.[23]

Results

Overall cancer risk

Results based on subgrouping by gender, age at entry to the cohort, and duration of follow-up are shown in Table 2. Separate analysis in patients aged younger than 20 years were not meaningful due to the small number of such patients. During the first year of observation, markedly increased RRs were found consistently across subgroups, but a decreasing trend was seen with increasing age at entry. Follow-up from one through nine years revealed RRs close to or slightly higher than unity. After 10 years or more, a significant deficit in the observed number of cancers was found in

Table 1. Number of patients given a discharge diagnosis of diabetes any time during 1965 through 1983 in the Uppsala Health Care Region of Sweden, by sex and age at entry into the cohort

Age	Females		Males	
	No.	Person-years	No.	Person-years
<20	784	8,397	803	8,352
20-39	1,588	15,899	1,814	16,885
40-59	3,503	28,106	4,853	35,717
>59	21,987	91,216	15,676	58,689
All ages	27,862	143,618	23,146	119,643

patients older than 60 years, the RR being 0.7 (CI = 0.6-0.9) in females and 0.6 (0.4-0.7) in males (Table 2). When the first year of observation was excluded from the analysis, the cumulative number of cancers observed was eight percent higher than expected in females (RR = 1.1, 1.0-1.1) and close to the expected in males (RR = 1.0, 0.9-1.1) (Table 3). A number of sites among both men and women were also significantly elevated.

Separate analyses confined to cohort members who had had DM as their primary or their only diagnosis on their first admission for diabetes revealed risk estimates almost identical to those shown in Table 2 in both sexes and at all periods of more than one year of follow-up; the difference in RR never exceeded 0.2 (data not shown). However, in patients with diabetes as their only diagnosis, the RR during the first year of observation was markedly lower: 1.7 in females and 2.1 in males.

Pancreatic cancer

We observed a marked seven- to ninefold increase in the incidence rates of pancreatic cancer during the first year of follow-up for both women and men. Following a one-year latency, the magnitude and the temporal pattern of the RR were similar in women and men, and the overall number of pancreatic cancers was 44 percent higher than expected (RR = 1.4, 1.2-1.7). An excess risk was still evident during years one through four (RR = 1.7; 1.4-2.1), and five through nine (RR = 1.3, 0.9-1.7) after entry to the cohort, but not thereafter (Table 4). The RRs were generally somewhat higher in patients aged 40-59 years than in those who were 60 years or older at start of follow-up (data not shown). Analysis confined to cohort members who had had diabetes as their primary or only discharge diagnosis revealed similar and slightly higher risk estimates as those in the entire cohort among both males and females and during various periods of follow-up (Table 5).

Table 2. The relative risk (RR) of developing any malignant disease in patients with diabetes mellitus, by sex, age at entry, and duration of follow-up in completed years

	Follow-up (years)				
	<1	1-4	5-9	10-19	1+
Females					
20-39	5.5[a]	1.0	1.4	0.5	0.9
40-59	4.1[a]	1.4[a]	1.2	1.0	1.2[a]
>59	2.8[a]	1.2[a]	0.9	0.7[a]	1.1
All ages	2.9[a]	1.2[a]	1.0	0.8[a]	1.1[a]
Males					
20-39	10.0[a]	1.4	1.1	1.5	1.3
40-59	5.5[a]	1.3	1.4[a]	1.2[a]	1.3[a]
>59	3.0[a]	1.1	0.8[a]	0.6[a]	0.9
All ages	3.2[a]	1.1[a]	0.9	0.8[a]	1.0

[a] 95% confidence intervals excluding 1.00.

Other gastrointestinal cancers

The RR of developing cancer in the esophagus, and the large bowel, but not in the stomach, were slightly higher in men than in women (Table 3). Apart from esophageal cancer, significantly increased risks by two- to threefold were seen for all these sites during the first year of observation (data not shown).

The risk of primary liver cancer showed a pattern similar to pancreatic cancer. Beside the marked 4.1 to 5.7 excess number of cases during the first year, a significant 89 to 106 percent increased risk persisted during one to four years of follow-up (Table 6). Generally, the RRs were higher in males than in females and they remained above unity throughout the period of follow-up. No single case occurred in patients younger than 40 years at entry, and there was no evidence of interaction with age in those who were 40-59 and 60 or older, respectively (data not shown).

Genito-urinary cancers

The risk of endometrial cancer was increased by 74 percent (RR = 1.7, 1.4-2.1) overall and by 47 percent (RR = 1.5, 1.2-1.8) when a one-year latency period was applied. A significant excess number of cases occurred during the first nine completed years of follow-up but not thereafter (Table 7). The pattern of change over time and the magnitude of the risk estimates was seemingly unrelated to age at start of follow-up (data not shown).

The cumulative number of prostatic cancers observed was significantly lower than the expected (RR = 0.7, 0.7-0.9) (Table 3). A 2.8 times increased risk during the first year, was followed by a significantly decreased RR at all subsequent periods of observation. Over time, this deficit increased from 20

Table 3. The relative risk (RR) of developing cancer one year or later following a first registration of diabetes mellitus, by site or type of cancer, and sex

ICD-7 Code	Site or type	Females				Males			
		Observed	Expected	RR	CI[a]	Observed	Expected	RR	CI[a]
140-209	All	1,294	1,203.3	1.1	1.0-1.1	1,123	1,129.3	1.0	0.9-1.1
150	Esophagus	9	11.0	0.8	0.4-1.6	22	14.2	1.6	1.0-2.4
151	Stomach	77	83.3	0.9	0.7-1.2	82	100.2	0.8	0.7-1.0
153	Colon	111	111.0	1.0	0.8-1.2	94	80.4	1.2	0.9-1.4
154	Rectum	47	52.4	0.9	0.7-1.2	73	54.5	1.3	1.1-1.7
155	Primary liver	85	65.5	1.3	1.0-1.6	59	33.0	1.8	1.4-2.3
157	Pancreas	88	59.5	1.5	1.2-1.8	68	49.1	1.4	1.1-1.8
162-163	All lung	46	41.0	1.1	0.8-1.5	106	112.0	1.0	0.8-1.1
170	Breast	240	260.5	0.9	0.8-1.1	2	1.5	1.3	0.2-4.8
171	Cervix uteri	21	29.3	0.7	0.4-1.1				
172	Corpus uteri	78	53.1	1.5	1.2-1.8				
175	Ovarian	51	59.9	0.9	0.6-1.1				
177	Prostate					224	302.9	0.7	0.7-0.9
178-179	Testis					7	7.4	1.0	0.4-2.0
180	Kidney	62	40.0	1.6	1.2-2.0	46	43.4	1.1	0.8-1.4
181	Bladder	28	30.2	0.9	0.6-1.3	70	69.4	1.0	0.8-1.3
190	Melanoma skin	12	17.6	0.7	0.4-1.2	13	13.7	1.0	0.5-1.6
191	Nonmelanoma skin	33	35.6	0.9	0.6-1.3	36	43.4	0.8	0.6-1.2
193	Nervous system	44	26.7	1.7	1.2-2.2	22	21.6	1.0	0.6-1.6
194	Thyroid	13	12.6	1.0	0.6-1.8	6	4.7	1.3	0.5-2.8
195	Endocrine gland	33	18.0	1.8	1.3-2.6	10	5.8	1.7	0.8-3.2
200-209	Hematopoietic system	77	78.4	1.0	0.8-1.2	79	81.3	1.0	0.8-1.2

[a] CI = 95% confidence interval.

to 50 percent (Table 7) and it was more pronounced at 60 years of age and older; the risk estimates in the age group 40-59 were, however, unstable due to small numbers (data not shown).

Table 4. The relative risk (RR) of developing pancreatic cancer in patients with diabetes mellitus, by sex and duration of follow-up

Follow-up (years)	Observed	Expected	RR	CI[a]
Females				
<1	88	11.8	7.5	6.0-9.2
1-4	58	31.5	1.8	1.4-2.4
5-9	23	18.2	1.3	0.8-1.9
10-19	7	9.4	0.7	0.3-1.5
≥1	88	59.5	1.5	1.2-1.8
Males				
<1	91	10.1	9.0	7.2-11.0
1-4	42	26.2	1.6	1.2-2.2
5-9	19	14.9	1.3	0.8-2.0
10-19	7	7.9	0.9	0.4-1.8
≥1	68	49.1	1.4	1.1-1.8
Both sexes				
<1	179	21.9	8.2	7.0-9.5
1-4	100	58.1	1.7	1.4-2.1
5-9	42	33.1	1.3	0.9-1.7
10-19	14	17.3	0.8	0.4-1.4
≥1	156	108.6	1.4	1.2-1.7

[a] CI = 95% confidence interval.

The RR of kidney cancer at one or more years of follow-up was increased in females (RR = 1.6, 1.2-2.0) but not in males (RR = 1.1, 0.8-1.4). There was no evidence of association between diabetes and bladder cancer (Table 3).

Other cancers

After one year of latency, the cumulative number of lung cancers was close to the expected in females

Table 5. The relative risk (RR) of developing pancreatic cancer in patients with diabetes mellitus, by sex and duration of follow-up; the effects of different restrictions of the cohort

Definition of the cohort		Follow-up (years)				
		<1	1-4	5-9	10-19	1+
All	Females	7.5[a]	1.8[a]	1.3	0.7	1.5[a]
	Males	9.0[a]	1.6[a]	1.3	0.9	1.4[a]
Diabetes as first discharge diagnosis	Females	8.8[a]	2.3[a]	1.5	0.9	1.8[a]
	Males	12.3[a]	1.6	1.3	1.1	1.4[a]
Diabetes as only discharge diagnosis	Females	9.6[a]	1.9	1.4	2.4	1.8[a]
	Males	14.8[a]	1.2	1.4	1.1	1.3

[a] 95% confidence intervals excluding 1.00.

Table 6. The relative risk (RR) of developing primary liver cancer in patients with diabetes mellitus, by sex and duration of follow-up

Follow-up (years)	Observed	Expected	RR	CI[a]
Females				
<1	51	12.4	4.1	3.0-5.4
1-4	65	34.3	1.9	1.5-2.4
5-9	14	20.4	0.7	0.4-1.2
10-19	6	10.8	0.6	0.2-1.2
≥1	85	65.5	1.3	1.0-1.6
Males				
<1	37	6.5	5.7	4.0-7.9
1-4	35	17.0	2.1	1.4-2.9
5-9	14	10.2	1.4	0.8-2.3
10-19	10	5.8	1.7	0.8-3.2
≥1	59	33.0	1.8	1.4-2.3
Both sexes				
<1	88	18.9	4.7	3.7-5.8
1-4	100	51.3	2.0	1.6-2.4
5-9	28	30.5	0.9	0.6-1.3
10-19	16	16.6	1.0	0.6-1.6
≥1	144	98.5	1.5	1.2-1.7

[a] CI = 95% confidence interval.

Table 7. The relative risk (RR) of developing endometrial and prostatic cancer in patients with diabetes mellitus, by duration of follow-up

Follow-up (years)	Observed	Expected	RR	CI[a]
Endometrial cancer				
<1	34	11.3	3.0	2.1-4.2
1-4	43	29.4	1.5	1.1-2.0
5-9	29	16.0	1.8	1.2-2.6
10-19	6	7.7	0.8	0.3-1.7
≥1	78	53.1	1.5	1.2-1.8
All years	112	64.4	1.7	1.4-2.1
Prostatic cancer				
<1	172	62.3	2.8	2.4-3.2
1-4	133	161.3	0.8	0.7-1.0
5-9	64	92.0	0.7	0.5-0.9
10-19	27	50.0	0.5	0.4-0.8
≥1	224	302.9	0.7	0.7-0.8
All years	396	365.2	1.1	1.0-1.2

[a] CI = 95% confidence interval.

(RR = 1.1) and somewhat lower than expected in males (RR = 1.0) (Table 3).

The incidence of malignant melanoma and nonmelanoma skin cancer was somewhat lower in the diabetes cohort than in the background population, whereas thyroid cancer and malignant diseases of the hematopoietic system occurred at about the expected rate. An excess number of tumors of endocrine glands (*e.g.* adrenal, parathyroid, pituitary) occurred in both females and males (Table 3).

Discussion

Few previous studies of diabetic patients have reported on overall cancer risk or risk for several major sites,[1,3,5] and some were based on small numbers of patients.[3,5] In the early study by Kessler,[1] in which mortality was used as the outcome measure, a significantly decreased risk (by 15 percent) in males and close to the expected number of cancer deaths in females were reported. Other studies generally found estimates close to unity with no appreciable difference by gender,[3] or higher risks in women than in men,[5] as in the present investigation.

The association between diabetes and pancreatic cancer has attracted most interest so far. The more important studies are characterized in Table 8. A markedly increased risk has been found in several case-control[2,5,6,8,24] and cohort[1,4,7] studies, whereas other authors did not confirm a significant association.[12-16] It is assumed generally that pancreatic cancer may cause diabetes due to malignant infiltration of the gland.[25] Because pancreatic cancer has a very rapid clinical course with a grim prognosis, it has been considered unlikely that preclinical pancreatic cancer would cause the onset of diabetes one year or more before detection of the malignant disease. Nevertheless, an excess risk of pancreatic cancer has been shown also following a one-year or longer latency period in several studies (Table 8). Our data extend previous observations of diabetes and pancreatic cancer. Beside confirming a high RR during the first year—due to selection bias (see below) and/or diabetes occurring as a consequence of the malignant disease—we found an excess risk which persisted at least 10 years after start of follow-up.

Whereas Kessler[1] found that the number of deaths from liver cancer (50 cases) was close to the expected (44.4 cases), a recent hospital-based case-control study reported a more than fourfold increased risk, seemingly more pronounced in patients receiving sulfonylurea treatment than in those managed by diet alone.[9] Our data are consistent with this finding, showing significantly increased risks in males and females even after one year of latency, notably within five years of follow-up. Chance is an unlikely explanation of these findings since the lower CI was 1.2 (Table 6). Alcohol abuse might be a common determinant for both diabetes[26] and hepatocellular cancer,[27] notably in males.

The excess risk of hepatocellular cancer is interesting, in view of the portal hyperinsulinemia characterizing overt and asymptomatic type 2 (non-insulin-dependent) DM. Insulin has growth-promoting effects exerted either by interaction with the specific insulin receptors or by cross-reactivity with IGF 1

Table 8. Published studies of pancreatic cancer in patients with diabetes mellitus

Study	Year	Study design	No. of cases	Overall	Relative risk by latency, years				Endpoint
					<1	1-4	5+	>1	
Kessler[1]	1970	Cohort	78	1.8					Mortality[e]
Wynder *et al*[2]	1973	Case-control							Incidence
Lin & Kessler[12]	1981	Case-control[a]	109[b]					0.8	Incidence
Ragozzino *et al*[3]	1982	Cohort	9	4.3				2.6	Incidence
Whittemore *et al*[4]	1983	Cohort	57			$P = 0.05$			Mortality
O'Mara *et al*[5]	1985	Case-control[b]	93					2.4[d]	Incidence
Gold *et al*[15]	1985	Case-control	201						Incidence
Norell *et al*[6]	1986	Case-control	99	3.3			2.4		Incidence
Mack *et al*[16]	1986	Case-control	490	1.3					Incidence
Hiatt *et al*[7]	1988	Cohort	48	4.5	7.6				Incidence
Cuzick *et al*[8]	1989	Case-control[a,c]	216	7.2			4.0	4.1	Incidence
Jain *et al*[24]	1991	Case-control	249			5.6	2.1[f]		Incidence
Present	1991	Cohort	335	2.7	8.2	1.8	1.2	1.5	Incidence

[a] Hospital controls.
[b] Including 15 islet cell cancers.
[c] Significant in females only.
[d] In females, RR = 0 in males.
[e] Crude calculated from table.
[f] 5-10 years RR 1.2 for more than 10 years.

receptors.[28] Similar mechanisms may be relevant for pancreatic cancer, since the exocrine pancreatic parenchyma is exposed to very high insulin concentrations through a portal circulation system from the insulin-producing pancreatic islets.[29] Moreover, the pancreatic islet somatostatin secretion is impaired in type 2 DM,[30] leading to diminished response of this hormone which has tumor-growth inhibitory effects.[31] *In vitro*, somatostatin has been shown to reverse cell growth in pancreatic cancer cells[32] and insulin-induced cell proliferation in human hepatoma cells.[33]

Data on the possible association between diabetes and endometrial cancer are equivocal.[34] Whereas several studies show a somewhat higher risk for endometrial cancer,[5,10,11] others report no increase in risk[1,34] including a Swedish study.[35] High levels of endogenous estrogens, a documented feature of diabetic women[5,36] and an established risk factor for endometrial cancer[34] is one explanation for such an association. Because one study reported a twofold increased risk which was unaltered after adjustment for body mass,[5] obesity may not be a confounder of such an association.

If DM were a causal risk factor for pancreatic, hepatocellular, and endometrial cancer, an RR which increases rather than decreases over time would have been expected. Therefore, our findings suggest that diabetes and these cancers may have etiologic factors in common. The diabetes diagnosis encompasses insulin-dependent and non-insulin-dependent forms, which according to current knowledge are likely to have different etiologies. However, given the age distribution of the patients with only 26 percent below the age of 60 and 10 percent under the age of 40, the vast majority of the patients are likely to have non-insulin-dependent DM. The onset of this disease is preceded by a long asymptomatic phase, characterized by insulin resistance, a compensatory hyperinsulinemia,[19] and various abnormalities in carbohydrate and lipid metabolism, as well as endocrine alterations. Further studies are required to identify dietary and other factors of etiologic importance for both diabetes mellitus and certain cancers.

An association between DM and prostatic cancer is identified for the first time, to our knowledge, in the present study. A few smaller studies showed risk estimates close to[1,5] or slightly higher[3] than unity. It is well known that the prevalence of palpable but undiagnosed (preclinical) prostatic cancer is high—0.1-7.6 percent[37]—among older men subjected to screening with digital rectal examination. Detection of such cancers among patients with diabetes at routine clinical examination is, therefore, a possible explanation for the almost threefold increased risk for the first year of follow-up. It is less clear whether advancement of diagnosis (lead time effect) in certain cases explains the whole pattern, with an early increase followed by a decrease and an overall RR close to unity. A rival interpretation would be that an early overdiagnosis of indolent cases precedes a true decrease in RR. A screening effect would entail that the observed incidence rate approaches the expected during the pro-

longed follow-up, notably in patients who are subjected to closer surveillance than the population at large. The decreasing rather than increasing RR over time therefore suggests that a causal relation might exist between diabetes and the reduced risk of prostatic cancer. Testosterone is generally assumed to be involved in malignant transformation of the prostate.[38] The plasma concentration of this hormone is decreased in adult men with DM and shows an inverse relationship to the degree of hyperglycemia.[20,39,40] Excessive concentrations of estrogens, which suppress the growth of many prostatic tumors, have been reported in diabetic men with or without coronary heart disease.[41]

We need to emphasize certain features and limitations of the study design. First, it is unknown to what extent the cohort recruited from inpatient discharges is representative of all patients with DM in the Uppsala region. Individuals with long-lasting disease and micro- or macroangiopathic complications are more likely to be treated as inpatients. If such features of the disease affect associations with any malignant disease, then generalization of our results must be made cautiously. Second, selection bias may occur because patients with diabetes who develop a cancer are more likely to become hospitalized than those without evidence of any malignant disease. For this reason, we restricted our results to one year after the first hospital admission which defined entry to the cohort. Bias may also be introduced if, for example, arteriosclerotic disease manifestations rather than diabetes were the main indication for hospitalization. Such diseases can be caused by smoking, obesity, and certain dietary patterns which are associated with the occurrence of several different cancers as well. Concerns over confounding by other diseases nevertheless may be groundless since no great changes in the risk estimates were revealed when more strict eligibility criteria were applied (Table 5). Finally, age at start of follow-up and duration of follow-up were defined by the date of first registration. When these measures were used as estimates of onset of disease, they would systematically misclassify those who had their first inpatient care due to diabetes prior to the start of the Inpatient Register in 1965. Thus, any trend in relation to age or follow-up will be underestimated.

It is concluded that specific surveillance with respect to early diagnosis of cancer does not seem justified in patients with DM. The present study design does not permit a separate analysis of cancer risk in type 1 and type 2 DM, which may differ in etiology and exposure to internal or environmental factors of importance for the initiation of cancer. However, biologically interesting associations may exist with a number of cancers, notably of the pancreas, liver, endometrium, and prostate. Future research should reassess these associations, analyze type 1 and type 2 DM separately, and take into account the possible biases and confounding factors which might have affected this study.

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