

Excess Risk of Primary Liver Cancer in Patients With Diabetes Mellitus

Hans-Olov Adami, Wong-Ho Chow, Olof Nyrén, Christian Berne, Martha S. Linet, Anders Ekblom, Alicja Wolk, Joseph K. McLaughlin, Joseph F. Fraumeni, Jr.*

Background: Chronic infection with hepatitis B virus, alcohol consumption, and cirrhosis of the liver are recognized risk factors for primary liver cancer. A few, but not all, studies have suggested that diabetes mellitus also increases risk for this cancer. **Purpose:** We conducted a population-based cohort study to analyze the risk of developing primary liver cancer and biliary tract (gallbladder, extrahepatic bile ducts, and ampulla of Vater) cancers among patients with diabetes. **Methods:** A cohort of 153 852 patients with a hospital discharge diagnosis of diabetes in the period from 1965 through 1983 was identified by use of the Swedish In-patient Register. Follow-up for these patients extended from the date of cohort entry through December 31, 1989. Incident cases of cancer during follow-up were identified through the Swedish Cancer Registry. To minimize the impact of selection bias, we excluded from the analysis patients who were diagnosed with liver and biliary tract cancers during the first year of follow-up. Standardized incidence ratios (SIRs) and their 95% confidence intervals (CIs) were computed by use of nationwide rates of liver and biliary tract cancers, adjusted for age, sex, and calendar year, for comparison. **Results:** During 1-24 years of follow-up, 819 incident cancers in the combined category of primary liver (n = 533) and biliary tract (n = 286) were identified in the cohort, yielding an overall SIR of 2.5 (95% CI = 2.3-2.6). The risk was higher in men (SIR = 3.2; 95% CI = 2.9-3.6) than in women (SIR = 2.0; 95% CI = 1.8-2.2). The incidence of primary liver cancer alone was increased fourfold (SIR = 4.1; 95% CI = 3.8-4.5); again, the risk was higher in men (SIR = 4.7; 95% CI = 4.2-5.2) than in women (SIR = 3.4; 95% CI = 2.9-3.9). Smaller increases in risk were seen for cancers of the gallbladder, the extrahepatic bile ducts, and the ampulla of Vater. After exclusion of diabetic patients with concomitant diseases that predispose to primary liver cancer, such as alcoholism, cirrhosis, and hepatitis, the persistence of an approximately threefold excess risk was observed. **Conclusions:** Our findings suggest that patients with diabetes are at increased risk of developing primary liver cancer and perhaps cancers of the biliary tract. The mechanisms involved in the association of diabetes and liver cancer remain to be clarified. Additional studies are needed to determine whether patients with insulin-dependent diabetes mellitus and those with non-insulin-dependent diabetes mellitus differ in their risk for primary liver

cancer or whether the risk is affected by the type of diabetes treatment. [J Natl Cancer Inst 1996;88:1472-77]

Chronic infection with hepatitis B virus is a dominant cause of primary liver cancer in developing countries, but risk factors for this cancer in Western populations are poorly understood, although alcohol consumption and cirrhosis play some role (1). A few (2-6) but not all (7) case-control and cross-sectional studies of liver cancer have suggested an association with diabetes mellitus, although cohort studies (8,9) have been inconclusive because of their limited size.

In a previous cohort study (10), we found a 50% excess risk for hepatobiliary cancer in patients 1 or more years after a hospital discharge diagnosis of diabetes, and we hypothesized that, in non-insulin-dependent diabetes mellitus, growth-promoting effects in the liver might occur through stimulation of insulin and insulin-like growth factor-1 (IGF-1) receptors as a consequence of elevated circulating levels of insulin or its precursors. However, we had limited power to assess risk after long-term follow-up, and we made no attempt to distinguish primary liver cancer from cancers of the biliary tract. Therefore, we carried out an expanded population-based cohort study, the largest to date, to analyze separately the risks for liver cancer and biliary tract cancers among patients with diabetes during long-term follow-up.

Patients and Methods

The Cohort

Because there is almost no private in-patient treatment in Sweden, hospital-provided medical services are, in effect, population based and referable to the county in which the patient lives. Beginning in 1964-1965, the Swedish National Board of Health and Welfare started collecting data on individual hospital discharges in the In-patient Register. In addition to a national registration number (a unique personal identifier assigned to all Swedish residents), each record in-

**Affiliations of authors:* H.-O. Adami, A. Ekblom, Department of Cancer Epidemiology, University Hospital, Uppsala, Sweden, and Department of Epidemiology, Harvard School of Public Health, Boston, MA; W.-H. Chow, International Epidemiology Institute, Rockville, MD, and Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD; O. Nyrén, A. Wolk (Department of Cancer Epidemiology), C. Berne (Department of Internal Medicine), University Hospital, Uppsala; M. S. Linet, J. F. Fraumeni, Jr., Division of Cancer Epidemiology and Genetics, National Cancer Institute; J. K. McLaughlin, International Epidemiology Institute.

Correspondence to: Professor Hans-Olov Adami, M.D., Ph.D., Department of Cancer Epidemiology, University Hospital, S-751 85 Uppsala, Sweden.
See "Notes" section following "References."

Table 1. Characteristics of patients with a hospital discharge diagnosis of diabetes mellitus in Sweden during the period from 1965 through 1983, with follow-up through 1989

| Characteristic | Men | Women |
|--|---------|---------|
| No. of patients | 73 847 | 80 005 |
| Total No. of person-years of follow-up | 497 825 | 539 592 |
| Average age at cohort entry, y | 60.5 | 65.2 |
| Average years of follow-up | 6.7 | 6.7 |
| Average calendar year at entry | 1977 | 1977 |
| No. of primary liver cancers (ICD-7 code 155.0)* | 427 | 242 |
| No. of extrahepatic liver cancers (ICD-7 codes 155.1-155.9)† | 107 | 287 |
| Average age at cancer diagnosis, y | 71.9 | 77.0 |

*One hundred thirty-six of these cancers (in 85 men and 51 women), diagnosed during the first year of follow-up, were excluded from all analyses. ICD-7 = International Classification of Diseases, seventh revision.

†One hundred eight of these cancers (in 25 men and 83 women), diagnosed during the first year of follow-up, were excluded from all analyses.

cludes data on hospital departments and up to eight discharge diagnoses, coded according to the seventh revision of the International Classification of Diseases (ICD-7) (11) through 1968 and according to the eighth revision (ICD-8) (12) thereafter. The number of hospitals delivering data to the register has increased steadily. In 1969, the register covered 60% of the Swedish population; in 1978, this percentage was 75%; by the end of 1983, it was 85%. This register was described in more detail previously (13).

We considered all records in the In-patient Register with a hospital discharge diagnosis of diabetes (ICD-7 code 260; ICD-8 code 250) and identified 216 827 unique national registration numbers with at least one such record for the period from 1965 through 1983. Record linkage to the nationwide registers of Total Population, Causes of Death, and Population Migration enabled us to exclude 25 415 records with incorrect national registration numbers that did not correspond to any living, deceased, or emigrated person. Inclusion of these records would have resulted in the contribution of additional person-years at no risk of cancer for all time through the end of follow-up.

Follow-up

We obtained information on dates and causes of death for deceased persons from the Register of Causes of Death and on dates of emigration for emigrated persons from the Register of Population Migration. Causes of death were coded according to ICD-8 (12) and ICD-9 (14). The national Swedish Cancer Registry, founded in 1958 and estimated to be 98% complete (15), was used to identify subjects with a prevalent cancer at the time of entry into the cohort and all incident cancers diagnosed in the cohort during follow-up.

The time of observation was calculated from the date of entry into the cohort (i.e., the date of discharge after the index hospitalization) until the occurrence of

a diagnosis of liver or biliary tract cancer, emigration, death, or the end of the observation period (December 31, 1989). We excluded 14 881 subjects who died during the index hospital admission and an additional 6606 subjects whose records revealed date inconsistencies during the record linkages. Among the remaining 169 925 subjects, 16 073 (9.5%) were excluded because of prevalent cancers, which left 153 852 patients in the cohort (Table 1).

Analyses

The Cancer Registry (16) has coded malignant diseases according to the ICD-7 classification scheme during the entire period under study. Liver and biliary tract cancer, ICD-7 code 155, is further subdivided to a four-digit level according to the anatomic locations shown in Table 2. Through 1969, only two four-digit codes were used, i.e., 155.0 (liver, primary) and 155.1 (biliary passages). From 1970, the latter code was subdivided into 155.1 (gallbladder), 155.2 (extrahepatic bile ducts), 155.3 (ampulla of Vater), 155.8 (multiple parts), and 155.9 (unspecified bile passages). The Cancer Registry also codes the histopathologic type of cancer, but the validity of this routinely collected information for liver cancer has never been reviewed.

To calculate the expected number of cancers, we multiplied the number of person-years for each sex by age-specific cancer incidence rates for each 5-year age group and calendar year of observation. These expected rates for liver and biliary tract cancer (ICD-7 code 155) and for cancers of the various subsites were derived from the entire Swedish population. In addition to the standard rates based on all diagnosed cases (and shown in the tables), we created age- and sex-specific rates that excluded cases first detected at autopsy. We also calculated expected numbers of deaths by using the same principles as used in the incidence analyses.

For the main analysis, we excluded the person-years that elapsed in the first year of follow-up and the liver cancer cases that were detected and the deaths that occurred in the same period in order to minimize the possible impact of selection bias. Such bias could occur if diabetes patients who become ill from liver cancer or die of any of the causes of interest within 1 year are more likely to be hospitalized than patients with diabetes in general. The ICD codes do not distinguish insulin-dependent from non-insulin-dependent diabetes mellitus, and the register provides no clinical data on, for example, medications or glycemic control. Instead, we made several attempts to separate these diseases through analyses stratified by age at entry, year of birth, and diabetes complications. Finally, certain diseases may be associated both with diabetes and with an elevated risk for liver cancer. A higher prevalence of such conditions in the diabetes cohort than in the general population would exaggerate our estimates of a relationship between diabetes and liver cancer. Therefore, in a separate analysis, we stratified the patients according to whether or not they had diagnoses of alcoholism, liver cirrhosis, hepatitis, hemochromatosis, or jaundice.

The standardized incidence ratio (SIR) or the standardized mortality ratio, defined as the ratio of observed number of cancers or deaths, respectively, to those expected, was used as a measure of relative risk. The 95% confidence interval (CI) for each ratio was calculated on the assumption that the observed number follows a Poisson distribution.

Table 2. Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) for primary liver and biliary tract cancers during 1-24 years of follow-up among patients with diabetes mellitus*

| ICD-7 code | Cancer sites† | Men | | | | Women | | | | Both sexes | | | |
|------------|-------------------------|-----|-------|------|---------|-------|-------|------|---------|------------|-------|------|---------|
| | | Obs | Exp | SIRs | 95% CIs | Obs | Exp | SIRs | 95% CIs | Obs | Exp | SIRs | 95% CIs |
| 155.0 | Liver, primary | 342 | 72.8 | 4.7 | 4.2-5.2 | 191 | 56.4 | 3.4 | 2.9-3.9 | 533‡ | 129.2 | 4.1 | 3.8-4.5 |
| 155.1 | Gallbladder | 38 | 31.6 | 1.2 | 0.9-1.7 | 143 | 105.4 | 1.4 | 1.1-1.6 | 181 | 137.0 | 1.3 | 1.1-1.5 |
| 155.2 | Extrahepatic bile ducts | 27 | 16.5 | 1.6 | 1.1-2.4 | 33 | 26.6 | 1.2 | 0.9-1.7 | 60 | 43.1 | 1.4 | 1.1-1.8 |
| 155.3 | Ampulla of Vater | 12 | 7.0 | 1.7 | 0.9-3.0 | 19 | 6.9 | 2.8 | 1.7-4.3 | 31 | 13.9 | 2.2 | 1.5-3.2 |
| 155 | All sites§ | 424 | 131.5 | 3.2 | 2.9-3.6 | 395 | 202.6 | 2.0 | 1.8-2.2 | 819 | 334.0 | 2.5 | 2.3-2.6 |

*ICD-7 = International Classification of Diseases, seventh revision; Obs = observed; Exp = expected.

†Through 1969, all cancers in biliary passages were coded as 155.1.

‡Histopathologic types: hepatocellular carcinoma (n = 387, 72.6%), cholangiocarcinoma (n = 56, 10.5%), adenocarcinoma NOS (not otherwise specified) (n = 86, 16.1%), unspecified epithelial tumors (n = 2, 0.4%), and malignant hemangioendothelioma (n = 2, 0.4%).

§Total numbers exceed slightly the sum of the four sites because some cancers had multiple (ICD-7 code 155.8) or unspecified (ICD-7 code 155.9) locations.

Results

The final study cohort, characterized in Table 1, comprised 73 847 men and 80 005 women, with mean ages at the start of follow-up of 60.5 years and 65.2 years, respectively. Only 13 216 (8.6%) of the cohort members were younger than 30 years of age at entry, whereas 7323 (4.8%) were 30-39 years of age at entry. A total of 669 primary liver cancers occurred in men and women during the 1 037 417 person-years of observation. The 136 primary liver cancers diagnosed during the first year after cohort entry (versus the 21.5 expected—yielding an SIR of 6.3 [95% CI = 5.3-7.5]) were excluded from further analysis. Similarly, of the 394 patients with biliary tract cancers, we excluded 108 who were diagnosed within the first year of follow-up.

During 1-24 years of follow-up, 819 incident cancers arose in the combined category of liver and biliary passages, yielding an overall SIR of 2.5 (95% CI = 2.3-2.6), with the risk being higher in men (SIR = 3.2; 95% CI = 2.9-3.6) than in women (SIR = 2.0; 95% CI = 1.8-2.2) (Table 2). The excess risk was similar for patients with and without any of the selected discharge diagnoses indicating diabetic complications (as a measure of disease severity) either at the index admission or at any hospital discharge during follow-up (data not shown). The incidence of primary liver cancer alone was increased fourfold (SIR = 4.1; 95% CI = 3.8-4.5), whereas smaller but significant increases in risk were seen for cancers of the gallbladder, extrahepatic bile ducts, and ampulla of Vater (Table 2). The SIR for primary liver cancer was higher in men (SIR = 4.7; 95% CI = 4.2-5.2) than in women (SIR = 3.4; 95% CI = 2.9-3.9). This difference and the larger proportion of liver cancer among men (80.7%) than

among women (48.4%) accounted for the higher risk in men when all hepatobiliary sites were combined. The distribution of tumors by histopathologic type, as reported to the Cancer Registry, showed a predominance of hepatocellular carcinoma (Table 2, ‡ footnote).

A substantial proportion of all primary liver cancers reported to the Cancer Registry (16) (about 32% in 1980 and 22% in 1989), including those in the diabetes cohort (49%), was first detected at autopsy. Because differences in autopsy frequency between patients hospitalized as a consequence of diabetes and the general population might bias the risk estimates, we recalculated the SIRs on the basis of observed and expected numbers of cancers diagnosed in living individuals. Compared with data shown in Table 2, the excess risk for liver cancer was only slightly reduced in both men (SIR = 3.7; 95% CI = 3.2-4.3) and women (SIR = 2.9; 95% CI = 2.4-3.6). The 259 cases observed among living patients were diagnosed at a mean age of 70.6 years in men and 75.7 years in women, and the distribution of tumors by histopathologic type resembled that shown for all patients in the series. In both sexes, the SIRs remained at about the same level during the follow-up period (Table 3). A similar temporal pattern was seen after exclusion of cases detected at autopsy (data not shown).

We made several attempts to distinguish patients with insulin-dependent diabetes mellitus from those with non-insulin-dependent diabetes mellitus. First, the relative risk of developing primary liver cancer was analyzed on the basis of the patient's age at cohort entry (start of follow-up). There was insufficient power to assess risks in younger individuals, but a clear excess was evident among men 40 years of age and older and among

Table 3. Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) for primary liver cancer (International Classification of Diseases, seventh revision [ICD-7] code 155.0) among patients with diabetes mellitus, by completed years of follow-up, age at the start of follow-up, year of birth, and diabetic complications*

| | Men | | | | Women | | | |
|------------------------------|-----|------|------|----------|-------|------|------|----------|
| | Obs | Exp | SIRs | 95% CIs | Obs | Exp | SIRs | 95% CIs |
| Completed years of follow-up | | | | | | | | |
| 1-4 | 146 | 30.2 | 4.8 | 4.1-5.7 | 85 | 23.5 | 3.6 | 2.9-4.5 |
| 5-9 | 122 | 29.4 | 4.2 | 3.5-5.0 | 71 | 23.0 | 3.1 | 2.4-3.9 |
| 10-14 | 59 | 10.1 | 5.9 | 4.5-7.5 | 28 | 7.6 | 3.7 | 2.5-5.4 |
| 15-24 | 15 | 3.2 | 4.8 | 2.7-7.8 | 7 | 2.4 | 3.0 | 1.2-6.1 |
| Age at start of follow-up, y | | | | | | | | |
| <30† | 1 | 0.2 | 5.0 | 0.1-27.7 | 0 | 0.2 | 0.0 | 0.0-19.0 |
| 30-39 | 2 | 0.4 | 4.6 | 0.5-16.7 | 1 | 0.3 | 3.7 | 0.1-20.5 |
| 40-49 | 17 | 2.2 | 7.6 | 4.4-12.1 | 2 | 0.9 | 2.3 | 0.3-8.3 |
| 50-59 | 66 | 10.2 | 6.5 | 5.0-8.2 | 18 | 4.0 | 4.6 | 2.7-7.2 |
| 60-69 | 123 | 25.3 | 4.9 | 4.1-5.8 | 43 | 12.9 | 3.3 | 2.4-4.5 |
| ≥70‡ | 133 | 34.5 | 3.9 | 3.2-4.6 | 127 | 38.2 | 3.3 | 2.8-4.0 |
| Year of birth | | | | | | | | |
| <1900 | 53 | 14.6 | 3.6 | 2.7-4.8 | 64 | 21.3 | 3.0 | 2.3-3.8 |
| 1900-1919 | 235 | 50.1 | 4.7 | 4.1-5.3 | 116 | 31.9 | 3.6 | 3.0-4.4 |
| 1920-1939 | 53 | 7.8 | 6.8 | 5.1-8.9 | 11 | 2.9 | 3.8 | 1.9-6.7 |
| ≥1940 | 1 | 0.4 | 2.8 | 0.0-15.4 | 0 | 0.3 | 0.0 | 0.0-13.1 |
| Diabetic complications§ | | | | | | | | |
| No | 317 | 66.7 | 4.8 | 4.2-5.3 | 183 | 52.0 | 3.5 | 3.0-4.1 |
| Yes | 25 | 6.1 | 4.1 | 2.7-6.1 | 8 | 4.4 | 1.8 | 0.8-3.6 |

*Obs = observed; Exp = expected.

†Mean age at entry, 18.7 years.

‡Mean age at entry, 77.5 years.

§ICD-7 codes: 260.99 (diabetes mellitus with multiple or unspecified complications), 788.60 (acetonemia without further specification), and 789.70 (acetonuria or ketonuria of unknown cause). International Classification of Diseases, eighth revision, codes: 250.08 (diabetes mellitus with other specified complications), 788.60 (acetonemia), 788.69 (acidosis without further specifications), and 789.60 (acetonuria or ketonuria of unknown cause).

women 50 years of age and older (Table 3). Second, risk was analyzed on the basis of the patient's year of birth, assuming that non-insulin-dependent diabetes mellitus predominated in the oldest birth cohort and insulin-dependent diabetes mellitus predominated in the youngest. Although an excess risk was clearly evident in the oldest cohorts—with a slightly increasing trend in SIR, notably among men—the numbers were too small to evaluate risk among cohort members born after 1940. Finally, we distinguished patients who ever had a hospital discharge diagnosis indicating diabetes-associated acidosis, as noted in the footnote (§) of Table 3. Among both men and women, the relative risk was higher in patients without than in those with any of the acute or chronic complications of diabetes.

We analyzed mortality from a large number of causes to determine if the excess incidence of liver cancer was reflected in the mortality pattern and to evaluate whether smoking and alcohol consumption might be more common among the cohort members than among the general population, from which the expected incidence and mortality rates were derived (Table 4). Mortality from lung cancer was close to expectation, as was its incidence (SIR = 1.2; 95% CI = 1.1-1.3), suggesting that confounding by smoking is unlikely in our data. In contrast, we found a threefold increased mortality from alcoholism and a fivefold excess of liver cirrhosis in both men and women (Table 4). There was also a marked excess of infections, including septicemia (Table 4) as well as tuberculosis and pneumonia (data not shown).

The mortality findings led us to divide the study cohort into two subgroups. One subgroup comprised 5517 men (7.5% of the men) and 1831 women (2.3% of the women) who also had alcoholism, liver cirrhosis, or other conditions that may predispose to primary liver cancer (Table 5). The overall relative risk for liver cancer in this subgroup was elevated more than 30-fold among men and almost 50-fold among women. The highest excess risks were seen in patients who had diabetes in combination with liver cirrhosis or hemochromatosis (Table 5). However, an approximately threefold, statistically significant increased risk for liver cancer persisted in diabetic patients without any prior hospital discharge diagnosis of conditions that are known to predispose to liver cancer (two-sided $P < .001$, based on the Poisson distribution).

Discussion

The salient finding in this large, population-based cohort study was a highly significant, fourfold risk for primary liver cancer among patients hospitalized with diabetes mellitus. Although slightly higher among men than among women, the excess risk was consistent in both sexes, in different age groups and birth cohorts, and throughout the follow-up period. We had limited ability to study risk by age at diabetes onset because inpatient care could have taken place before the registration system started and because many patients may have been hospitalized only after complications developed, perhaps many years after the initial diagnosis. However, it can be inferred from the average age and average calendar year at cohort entry (Table 1) that most patients were born before 1920. Because relatively few patients with insulin-dependent diabetes mellitus in these birth cohorts ever reached the age of 60, our results pertain mainly to patients with non-insulin-dependent diabetes mellitus.

Chance is an unlikely explanation for our findings because of the high statistical significance of the results. Differential misclassification of outcome, with more complete ascertainment of liver cancer in diabetic patients, is also an unlikely explanation because liver cancer rarely escapes medical attention, difficulties in differential diagnosis should influence those with and without diabetes equally, the excess risk persisted after the exclusion of cases diagnosed first at autopsy, and notification to the Swedish Cancer Registry is close to 100% complete (16). We believe that selection bias was minimized because of the complete follow-up and the 1-year latency after entry into the cohort. Liver cancer usually has a rapidly fatal course, and it is therefore unlikely to be symptomatic more than 1 year prior to diagnosis.

Confounding is a more serious concern, particularly since high consumption of alcohol predisposes individuals to hepatocellular carcinoma, often with cirrhosis as an intermediate step (17), and alcoholism was overrepresented as a cause of death in our cohort. In contrast to some earlier reports, recent studies (18,19) have suggested that heavy consumption of alcohol is not associated with an excess risk of diabetes, whereas moderate consumption of alcohol may actually lower the risk. Therefore,

Table 4. Standardized mortality ratios (SMRs) with 95% confidence intervals (CIs) during 1 to 24 years of follow-up for selected causes of death among patients with diabetes mellitus*

| Cause of death | Men | | | | Women | | | |
|----------------------|------|--------|------|-----------|-------|--------|------|-----------|
| | Obs | Exp | SMRs | 95% CIs | Obs | Exp | SMRs | 95% CIs |
| All cancers | 3815 | 3116.2 | 1.2 | 1.19-1.26 | 3511 | 2891.8 | 1.2 | 1.17-1.25 |
| Lung cancer | 594 | 525.0 | 1.1 | 1.0-1.2 | 190 | 182.5 | 1.0 | 0.9-1.2 |
| Primary liver cancer | 271 | 80.2 | 3.4 | 3.0-3.8 | 161 | 70.0 | 2.3 | 2.0-2.7 |
| Biliary cancer† | 76 | 60.8 | 1.3 | 1.0-1.6 | 187 | 150.6 | 1.2 | 1.1-1.4 |
| Alcoholism | 182 | 49.8 | 3.7 | 3.2-4.2 | 20 | 6.1 | 3.3 | 2.0-5.1 |
| Liver cirrhosis | 645 | 112.6 | 5.7 | 5.3-6.2 | 319 | 65.9 | 4.8 | 4.3-5.4 |
| Infection | 238 | 94.9 | 2.5 | 2.2-2.9 | 272 | 103.5 | 2.6 | 2.3-3.0 |
| Septicemia | 97 | 29.0 | 3.4 | 2.7-4.1 | 116 | 32.5 | 3.6 | 3.0-4.3 |

*Obs = observed; Exp = expected.

†International Classification of Diseases, seventh revision, codes: 155.1, 155.2, and 155.8; International Classification of Diseases, eighth and ninth revisions, code: 156.

Table 5. Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) for primary liver cancer (International Classification of Diseases, seventh revision, code 155.0) among patients with diabetes mellitus, with or without conditions that may predispose to liver cancer*

| Other diseases | Men | | | | | Women | | | | |
|-----------------|---------------|-----|------|-------|------------|---------------|-----|------|------|-----------|
| | No. in cohort | Obs | Exp | SIRs | 95% CIs | No. in cohort | Obs | Exp | SIRs | 95% CIs |
| Alcoholism | | | | | | | | | | |
| No | 69 340 | 267 | 69.7 | 3.8 | 3.4-4.3 | 79 260 | 177 | 56.1 | 3.2 | 2.7-3.7 |
| Yes | 4507 | 75 | 3.1 | 23.8 | 18.7-29.9 | 745 | 14 | 0.3 | 47.4 | 25.9-79.6 |
| Cirrhosis | | | | | | | | | | |
| No | 71 857 | 242 | 71.5 | 3.4 | 3.0-3.8 | 78 999 | 147 | 55.9 | 2.6 | 2.2-3.1 |
| Yes | 1990 | 100 | 1.3 | 74.7 | 60.7-90.8 | 1006 | 44 | 0.5 | 84.1 | 6.1-112.8 |
| Hepatitis | | | | | | | | | | |
| No | 73 740 | 339 | 72.7 | 4.7 | 4.2-5.2 | 79 899 | 190 | 56.4 | 3.4 | 2.9-3.9 |
| Yes | 107 | 3 | 0.1 | 36.4 | 7.3-106.3 | 106 | 1 | 0.1 | 12.9 | 0.2-71.7 |
| Hemochromatosis | | | | | | | | | | |
| No | 73 799 | 337 | 72.8 | 4.6 | 4.2-5.2 | 79 987 | 191 | 56.4 | 3.4 | 2.9-3.9 |
| Yes | 48 | 5 | 0.0 | 106.5 | 34.3-248.5 | 18 | 0 | 0.0 | 0.0 | 0.0-404.5 |
| Jaundice | | | | | | | | | | |
| No | 73 405 | 332 | 72.4 | 4.6 | 4.1-5.1 | 79 680 | 187 | 56.2 | 3.3 | 2.9-3.8 |
| Yes | 442 | 10 | 0.5 | 21.8 | 10.4-40.0 | 325 | 4 | 0.2 | 16.7 | 4.5-42.8 |
| Any | | | | | | | | | | |
| No | 68 330 | 219 | 68.7 | 3.2 | 2.8-3.6 | 78 174 | 142 | 55.4 | 2.6 | 2.2-3.0 |
| Yes | 5517 | 123 | 4.1 | 30.3 | 25.2-36.1 | 1831 | 49 | 1.0 | 47.4 | 36.6-65.3 |

*Obs = observed; Exp = expected.

alcoholism may not be a strong confounder in the relationship between diabetes and liver cancer. Indeed, the excess risk for liver cancer was greater among patients with diabetes than among Swedish hospital patients with a discharge diagnosis of alcoholism (17). Moreover, analyses confined to diabetic patients without any of the hospital discharge diagnoses of conditions associated with primary liver cancer, notably liver cirrhosis, revealed a highly significant 2.6-fold to 3.2-fold increased risk in both men and women.

Several mechanisms may explain the association between diabetes and primary liver cancer. Increased cell proliferation is probably important in the development of at least some human cancers (20,21) and may contribute to the excess risk for hepatocellular cancer in patients with chronic hepatitis B virus infection, alcoholic liver disease, and liver cirrhosis (21,22). Patients with non-insulin-dependent diabetes mellitus are characterized by insulin resistance, compensatory hyperinsulinemia, and increased growth factor production (23,24). Hence, liver cells are directly exposed via the portal circulation to high levels of insulin produced by the pancreas. Furthermore, the onset of clinical diabetes is preceded by years of chronic hyperinsulinemia, with an elevated proportion of proinsulin and split products of proinsulin, molecules with some homology to IGF-1 (25). Insulin or its precursors have been shown to interact with liver cells and to stimulate mitogenesis or carcinogenesis (26-28). The slightly higher risk among men than among women is paralleled by higher plasma insulin concentrations in men than in women (29,30).

In addition, diabetes has been associated with an increased risk for chronic liver disease, including cirrhosis and fatty liver, particularly among obese patients (31,32). Liver cancer occurs excessively in patients with cirrhosis that is associated with hepatitis B or C virus infection and with heavy consumption of alcohol (3,17,33). Further studies are needed to clarify whether

these risk factors are involved or whether liver cancer is simply a consequence of the cirrhotic process that may complicate diabetes and related obesity. For some cohort members, however, non-insulin-dependent diabetes mellitus may actually be secondary to alcohol-induced or other types of progressive liver disease that can reduce insulin sensitivity and secretion (3,34,35). Although the absolute number of excess deaths from liver cirrhosis was small, its impact may be substantial, since less severe forms of cirrhosis are often not diagnosed (36). Careful interpretation is warranted, however, because an association may arise spuriously if diabetic patients with concomitant liver cirrhosis (or alcoholism) are more likely to be hospitalized than those with diabetes alone (37).

In contrast to the elevated risk for primary liver cancer, weaker (though statistically significant) associations were found between diabetes and cancers of the biliary tract. These associations, if confirmed, are probably mediated by the twofold to threefold risk of gallstones reported in patients with insulin-dependent and non-insulin-dependent diabetes mellitus (38), since gallstones are associated with an excess risk for cancers of the gallbladder (39) and the extrahepatic bile ducts (40). In diabetic patients, gallbladder emptying is reduced, especially if associated with autonomic neuropathy (38), promoting biliary stasis and bacterial overgrowth that, in turn, promote the development of stones. The resulting mechanical trauma, infection, and chronic inflammatory process (40) have been implicated in biliary carcinogenesis, perhaps as a result of increased mitotic activity (20), although additional mechanisms may be required for cancer initiation (21). It is possible, however, that some biliary tract cancers may have arisen spuriously as a result of misclassification of liver cancers or pancreatic cancers, which also arise excessively in this cohort (41). Both liver and pancreatic tumors tend to be diagnosed at an advanced stage, when the exact site and origin may be difficult to find. In a

