Alcohol abuse and the risk of pancreatic cancer

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Background: Although most epidemiological studies do not support a role for alcohol in the aetiology of pancreatic cancer, an increased risk among heavy drinkers cannot be excluded.

Methods: In a retrospective cohort based on the Swedish Inpatient Register, we analysed the risk of pancreatic cancer among patients admitted to hospital for alcoholism (n=178 688), alcoholic chronic pancreatitis (n=3500), non-alcoholic chronic pancreatitis (n=4952), alcoholic liver cirrhosis (n=13 553), or non-alcoholic liver cirrhosis (n=7057) from 1965 to 1994. Follow up through to 1995 was accomplished by linkage to nationwide registers. Standardised incidence ratios (SIRs) express the relative risks by taking the general Swedish population as reference. To minimise the possible influence of selection bias, we excluded the first year observations.

Results: Alcoholics had only a modest 40% excess risk of pancreatic cancer (SIR 1.4, 95% confidence interval (CI) 1.2–1.5). Overrepresented smokers among alcoholics might confound a true SIR of unity among alcoholics to 1.4. SIR among alcoholic chronic pancreatitis patients (2.2, 95% CI 1.0–4.5) was considerably lower than that among non-alcoholic chronic pancreatitis patients (8.7, 95% CI 6.8–10.9), and decreased with increasing duration of follow up in both groups, indicating that most of the excess might be explained by reversed causation from undiagnosed cancers. Among patients with alcoholic cirrhosis, the increased risk of pancreatic cancer was also moderate (SIR 1.9, 95% CI 1.3–2.8) while no significant excess risk was found among non-alcoholic liver cirrhosis patients (SIR 1.2, 95% CI 0.6–2.2).

Conclusions: The excess risk for pancreatic cancer among alcoholics is small and could conceivably be attributed to confounding by smoking.

PATIENTS AND METHODS

The methodology used for the record linkage study based on the Swedish Inpatient Register has been described in detail elsewhere. In brief, the National Board of Health and Welfare started collecting data on individual hospital discharges in the Inpatient Register in 1964–65. In addition to the national registration number, a unique personal identifier assigned to all Swedish residents, each record contains administrative and medical data, such as hospital department and discharge diagnoses. Record linkage of the study cohort to the nationwide Register of Causes of Death allowed us to obtain information on date of death among those deceased up to 1995. Corresponding linkage to the Emigration Register identified dates of emigration, when applicable. The National Swedish Cancer Register, founded in 1958 and close to 98% complete, was used to ascertain all incident cancers. To remove records with incorrect national registration numbers, for which no matches would be expected on record linkages and which would contribute person time without any outcome, we also linked the cohorts to the Register of the Total Population.

We excluded records: (1) with erroneous or incomplete national registration numbers; (2) with inconsistencies uncovered during record linkage; (3) of patients who died during the index hospitalisation; and (4) of patients with prevalent cancers at entry. Records deleted as a result of the first two reasons listed were unlikely to be followed up, as indicated by the fact that only four pancreatic cancer cases were ascertained among 10 749 deleted records. Following these exclusions, we identified 178 688 patients with a discharge diagnosis of alcoholism (ICD-7=307, 322; ICD-8=291, 303; ICD-9=291, 303, 305A), 8452 for chronic pancreatitis (ICD-7=587.10, 587.19, ICD-8=577.10, 577.19; ICD-9=577B), 13 553 for alcoholic liver cirrhosis (ICD-7=581.10, ICD-8=571.00; ICD-9=571C, 571D), and 7057 for non-alcoholic liver cirrhosis (ICD-7=581.00, 583.10; ICD-8=571.01, 571.90, 571.98; ICD-9=571A, 571F, 571G), during 1965–1994. The chronic pancreatitis cohort was further subdivided into alcoholic or non-alcoholic subgroups according to a documented hospitalisation for alcoholism.

We only considered first primary cancers. Follow up time (person years) was therefore calculated from the first hospitalisation for the disease under study until the occurrence of a first cancer diagnosis, emigration, death, or the end of the observation period (31 December 1995), whichever occurred first. As these five cohorts partly overlapped, 10 075 patients were transferred from the alcoholism cohort to the

Abbreviations: SIRs, standardised incidence ratios.
appropriate alcoholism plus complication cohort when the complication was first diagnosed. Patients with both chronic pancreatitis and liver cirrhosis were allocated to the chronic pancreatitis cohorts. To minimise the possible influence of selection bias, we discarded person time and cancer cases occurring within the first year of follow up. To avoid possible ascertainment bias associated with differential autopsy rates between alcoholics and the general population, we did not count the first primary cancers found incidentally at autopsy. The expected number of cancers was calculated by multiplying the number of observed person years in age (five year groups), sex, and calendar year strata by the corresponding stratum specific cancer incidence rates, derived from the entire Swedish population. The incidence rates were aggregated by five calendar years to avoid instability of rare cancers. The relative risk of cancer was estimated as the standardised incidence ratio (SIR), defined as the ratio of the observed number of cancers to that expected. The 95% confidence interval (CI) of the SIR was calculated on the assumption that the observed number follows a Poisson distribution. We also stratified the analyses by selected cohort characteristics that may influence risk patterns, including age at first hospitalisation for the disease under study and follow up duration. A χ² statistic was used to test any monotonic trend of SIRs.

We also used an indirect method to evaluate the confounding effect of smoking. Let I be the pancreatic cancer incidence rate among non-smokers; RR the relative risk of pancreatic cancer associated with ever smoking; PY the observed person years; P1 the percentage of ever smokers among alcoholics; and P2 that among the general population. Assuming similar distributions of other risk factors for pancreatic cancer among alcoholics and the general population, and the fact that the ratio of observed person years in non-smoker and smoker subgroups can be reasonably approximated by the percentage of non-smokers and ever smokers, the observed number of cases can be approximated as I × PY × (1 + RR × P1 − P1), and the expected number of cases as I × PY × (1 RR × P2 − P2). The SIR associated with confounding of smoking can be approximated as (1 + RR × P1 − P1)/(1 + RR × P2 − P2).

RESULTS
Alcoholism cohort
Mean age at index hospitalisation for alcoholism in our study was 44 years, and mean duration of follow up was 10 years, yielding a total of 1 789 693 person years at risk (table 1).

We identified 305 pancreatic cancer cases after the first year from the index discharge, while 222 were expected, rendering a statistically significant 40% excess risk. The point estimate of the relative risk was a little higher among women than men although the difference was not statistically significant. We did not find any obvious variation in relative risk over 1–30 years of follow up. However, the excess risk increased with decreasing age at index hospitalisation (p value for trend 0.02). Comorbid diabetes mellitus did not importantly modify the relative risk (table 2).

Chronic pancreatitis cohorts
We identified 3050 and 4952 patients hospitalised for alcoholic chronic pancreatitis and non-alcoholic chronic pancreatitis, respectively. Mean age at first hospitalisation among members of the former cohort was 10 years younger than that in the latter cohort. The mean follow up time in both cohorts was approximately eight years (table 1). A more than twofold excess risk of pancreatic cancer was observed in the alcoholic chronic pancreatitis cohort (SIR 2.2, 95% CI 0.9–4.5) based on seven observed cases. The excess risk was higher among females than males. Patients with non-alcoholic chronic pancreatitis had a markedly greater excess risk for pancreatic cancer (SIR 8.7, 95% CI 6.8–10.9). However, relative risks fell significantly with increasing follow up duration in both cohorts, notably during the first years of follow up (SIR 3.6 for the alcoholic chronic pancreatitis cohort; SIR 28.8 for the non-alcoholic chronic pancreatitis cohort during the second and third years of observation). Neither cohort exhibited an obvious trend of relative risks by age at index hospitalisation. Comorbid diabetes mellitus did not materially modify the relative risk in the non-alcoholic chronic pancreatitis cohort while the number of alcoholic chronic pancreatitis patients with diabetes mellitus was too small to allow a stable stratified analysis (table 2).

Liver cirrhosis cohorts
A total of 13 553 and 7057 patients hospitalised for alcoholic liver cirrhosis and non-alcoholic liver cirrhosis were ascertained through the Swedish Inpatient Register. Mean ages at first hospitalisation were 56 and 58 years, respectively. Mean duration of follow up in both cohorts was shorter than that in the alcoholism or chronic pancreatitis cohorts (table 1). Compared with the Swedish general population, an approximate twofold risk for pancreatic cancer was observed among patients with alcoholic liver cirrhosis (SIR 1.9, 95% CI 1.3–2.8) whereas the corresponding relative risk among non-alcoholic liver cirrhosis patients was close to unity (SIR 1.2, 95% CI 0.6–2.2). Among alcoholic liver cirrhosis patients, the risk pattern did not differ appreciably by sex, follow up duration, or age at entry. Comorbid diabetes mellitus did not modify the relative risk in the alcoholic liver cirrhosis cohort (table 2).

DISCUSSION
Compared with the general population, alcoholic patients without alcoholic chronic pancreatitis or alcoholic liver
Table 2  Standardised incidence ratios (SIR) and 95% confidence intervals (CI) for pancreatic cancer among patients who were hospitalised for alcoholism, alcoholic chronic pancreatitis, non-alcoholic chronic pancreatitis, alcoholic liver cirrhosis, and non-alcoholic liver cirrhosis during 1965–1994, Sweden*

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Alcoholism</th>
<th>Alcohol chronic pancreatitis</th>
<th>Non-alcoholic chronic pancreatitis</th>
<th>Alcoholic liver cirrhosis</th>
<th>Non-alcoholic liver cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs†</td>
<td>SIR 95%CI</td>
<td>Obs† SIR 95%CI</td>
<td>Obs† SIR 95%CI</td>
<td>Obs† SIR 95%CI</td>
</tr>
<tr>
<td>Total</td>
<td>305</td>
<td>1.4-1.5</td>
<td>7 2.2 0.9-4.5</td>
<td>74 8.7 6.8-10.9</td>
<td>27 1.9 1.3-2.8</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>Male 1.3-1.5</td>
<td>4 1.4 0.4-3.7</td>
<td>51 9.9 7.4-13.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female 1.6-2.1</td>
<td>3 7.3 1.5-21.4</td>
<td>23 6.7 4.3-10.1</td>
</tr>
<tr>
<td>p value</td>
<td>0.25</td>
<td></td>
<td></td>
<td>0.02</td>
<td>0.11</td>
</tr>
<tr>
<td>Follow up duration (y)</td>
<td></td>
<td></td>
<td>Male 1.3-1.5</td>
<td>1 0.9 0.02-5.0</td>
<td>6 2.1 0.8-4.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female 1.6-2.1</td>
<td>2 0.2-7.2</td>
<td>12 4.5 2.3-7.9</td>
</tr>
<tr>
<td>p value for trend</td>
<td>0.35</td>
<td></td>
<td></td>
<td>0.16</td>
<td>0.01</td>
</tr>
<tr>
<td>Age at index discharge (y)</td>
<td></td>
<td></td>
<td>Male 1.3-1.5</td>
<td>1 0.9 0.02-5.0</td>
<td>6 2.1 0.8-4.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female 1.6-2.1</td>
<td>2 0.2-7.2</td>
<td>12 4.5 2.3-7.9</td>
</tr>
<tr>
<td>p value for trend</td>
<td>0.35</td>
<td></td>
<td></td>
<td>0.16</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes mellitus†</td>
<td></td>
<td></td>
<td>Male 1.3-1.5</td>
<td>1 0.9 0.02-5.0</td>
<td>6 2.1 0.8-4.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female 1.6-2.1</td>
<td>2 0.2-7.2</td>
<td>12 4.5 2.3-7.9</td>
</tr>
<tr>
<td>p value</td>
<td>0.35</td>
<td></td>
<td></td>
<td>0.16</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Excluding the first year of follow up.
†Observed number of cancer cases.‡Person time before the onset of diabetes mellitus was allocated to non-diabetes mellitus stratum.
prospective study design, a near complete follow-up, and a
much larger sample size than in previous studies. Possible
selection bias was minimised as the first year of follow up was
excluded. Despite the advantages of our study, register based
studies also have limitations apart from lack of information on
possible confounding factors. A mixture of exposed subjects in
the “unexposed” reference category by using the general
population as reference could lead to underestimation of the
excess risk for pancreatic cancer. Hence alcohol is unlikely to play
a causal role in the aetiology of pancreatic cancer.

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