PANCREATIC DISEASE

Alcohol abuse and the risk of pancreatic cancer

W Ye, J Lagergren, E Weiderpass, O Nyrén, H-O Adami, A Ekblom

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See end of article for authors' affiliations

Correspondence to:
Dr W Ye, Department of
Medical Epidemiology,
Karolinska Institutet, Box
281, SE 171 77,
Stockholm, Sweden;
weiy@mbbox.ki.se

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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 approximately 1.4. SIR among alcoholic chronic pancreatitis patients (2.2, 95% CI 0.9–4.5) 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 liver 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.

It has not been firmly established whether or not alcohol intake is causally related to pancreatic cancer. A number of studies have tried to address the relation between alcohol intake and risk of pancreatic cancer, and most showed a negative result.^{1–3} However, heavy alcohol intake may cause chronic pancreatitis,⁴ which has been indicated as a risk factor for pancreatic cancer.⁵ Alcohol may also alter pancreatic function by mechanisms other than alcohol related pancreatitis, and this may in turn predispose to pancreatic cancer.² If alcohol is indeed a risk factor for pancreatic cancer, this association should be easiest to document among subjects with a high and long term intake, notably among alcoholics. We therefore conducted a large population based cohort study, based on the Swedish Inpatient Register, of the risk of pancreatic cancer among patients with a discharge diagnosis of alcoholism, alcoholic chronic pancreatitis, or alcoholic liver cirrhosis. Pancreatic cancer risk was also evaluated in cohorts of patients hospitalised for non-alcoholic chronic pancreatitis or non-alcoholic liver cirrhosis.

PATIENTS AND METHODS

The methodology used for the record linkage study based on the Swedish Inpatient Register has been described in detail elsewhere.⁶ 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,⁷ 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.

Table 1 Distribution of patients and person years by sex and selected characteristics

	Alcoholism	Alcoholic chronic pancreatitis	Non-alcoholic chronic pancreatitis	Alcoholic liver cirrhosis	Non-alcoholic liver cirrhosis
No of patients	178 688	3500	4952	13 553	7057
Males	142 727	2976	3033	10 292	3369
Females	35 961	524	1919	3261	3688
Total person years of follow up	1 789 693	29 089	39 707	67 607	43 460
Person years at 1st year of follow up	173 483	3345	4545	11 128	6043
Average age at entry (y)	44.4	46.5	56.2	55.9	58.3
Average follow up (y)	10.2	8.3	8.0	5.0	6.2
Total No of pancreatic cancers	329	18	253	39	23
No of pancreatic cancers during 1st year of follow up	24	11	179	12	12
Average age at diagnosis of pancreatic cancer after 1st year of follow up (y)	64.1	58.0	64.6	66.9	70.0

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.^{8,9} 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 χ^2 statistic was used to test any monotonic trend of SIRs.⁹

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 $I \times PY \times (1 + RR \times P1 - P1)$, and the expected number of cases as $I \times PY \times (1 + RR \times P2 - P2)$. The SIR associated with confounding of smoking can be approximated as $(1 + RR \times P1 - P1) / (1 + RR \times P2 - P2)$.

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 3500 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*

Determinant	Alcoholism			Alcoholic chronic pancreatitis			Non-alcoholic chronic pancreatitis			Alcoholic liver cirrhosis			Non-alcoholic liver cirrhosis		
	Obs†	SIR	95%CI	Obs†	SIR	95%CI	Obs†	SIR	95%CI	Obs†	SIR	95%CI	Obs†	SIR	95%CI
Total	305	1.4	1.2–1.5	7	2.2	0.9–4.5	74	8.7	6.8–10.9	27	1.9	1.3–2.8	11	1.2	0.6–2.2
Sex															
Male	254	1.3	1.2–1.5	4	1.4	0.4–3.7	51	9.9	7.4–13.1	22	2.0	1.3–3.1	5	1.2	0.4–2.8
Female	51	1.6	1.2–2.1	3	7.3	1.5–21.4	23	6.7	4.3–10.1	5	1.6	0.5–3.7	6	1.3	0.5–2.8
p value		0.25			0.02			0.11			0.62			0.90	
Follow up duration (y)															
1–4	82	1.3	1.0–1.6	4	3.8	1.0–9.6	56	18.0	13.6–23.4	9	1.5	0.7–2.9	3	0.8	0.2–2.3
5–9	91	1.4	1.1–1.7	2	2.0	0.2–7.2	12	4.5	2.3–7.9	13	3.1	1.7–5.3	1	0.4	0.01–2.2
10+	132	1.5	1.2–1.8	1	0.9	0.02–5.0	6	2.1	0.8–4.7	5	1.3	0.4–3.0	7	2.8	1.1–5.7
10–14	78	1.5	1.2–1.9												
15–30	54	1.4	1.1–1.8												
p value for trend		0.35			0.16			<0.01			0.99			0.04	
Age at index discharge (y)															
<50	107	1.7	1.4–2.1	2	1.7	0.2–6.2	9	8.1	3.7–15.4	3	1.7	0.3–4.8	1	0.9	0.02–4.8
50–59	91	1.2	1.0–1.5	4	3.5	0.9–8.9	24	10.0	6.4–14.9	13	2.9	1.5–4.9	4	1.8	0.5–4.6
60–69	81	1.3	1.1–1.6	1	1.5	0.04–8.2	32	11.9	8.1–16.7	8	1.5	0.6–2.9	5	1.6	0.5–3.7
≥70	26	1.1	0.7–1.6	0	—	—	9	3.8	1.8–7.3	3	1.4	0.3–4.1	1	0.4	0.01–2.4
p value for trend		0.02			0.77			0.12			0.35			0.50	
Diabetes mellitus†															
No	282	1.4	1.2–1.5	7	3.2	1.3–6.6	63	8.8	6.8–11.3	21	1.8	1.1–2.8	8	1.1	0.5–2.1
Yes	23	1.7	1.1–2.6	0	—	—	11	7.7	3.9–13.8	6	2.4	0.9–5.2	3	2.1	0.4–6.1
p value		0.29			0.07			0.68			0.56			0.32	

* 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.

cirrhosis had a modest 40% excess risk for pancreatic cancer. Even among alcoholics who were diagnosed with chronic pancreatitis or liver cirrhosis, only twofold risks for pancreatic cancer were observed whereas a substantial but transient risk increase was found among non-alcoholic chronic pancreatitis patients. The remarkable excess risks during the first few years of follow up suggest that in some instances pancreatitis may be an early manifestation of an as yet undiagnosed pancreatic cancer. This would be an example of reversed causation or selection bias rather than a true causal association between pancreatitis and pancreatic cancer, as also indicated in our previous study.¹⁰ The relative risk of pancreatic cancer among non-alcoholic liver cirrhosis patients was close to unity.

As stated in several reviews,^{1–3} most previous epidemiological studies could not demonstrate an excess risk for pancreatic cancer associated with moderate alcohol intake. Recent studies corroborate these findings.^{11–18} In contrast, heavy alcoholic intake has been associated with an increased risk of pancreatic cancer in seven studies.^{19–26} A summary estimate of the relative risk among alcoholics or populations with heavy alcohol intake, mostly based on mortality data and small sample sizes, indicates a non-significant standardised mortality ratio of approximately 1.2.³ More recent studies of alcoholics based on incident cases show higher relative risks (SIR 1.3–2.6).^{27–29} In a cohort study among alcohol abstainers, a significantly reduced risk of pancreatic cancer was found, although the confounding effect of smoking was not controlled for in the analysis.³⁰ Selection bias due to low participation rate, recall bias, and chance finding as a result of small sample size may be some of the reasons for these discrepant results.

The most serious limitation of our study was the lack of information on smoking, an established risk factor for pancreatic cancer.³¹ The habit is clearly overrepresented in alcoholics. We estimated to what extent confounding by smoking might generate the 40% overall excess risk we found among patients with alcoholism. Assuming a relative risk of 2 for pancreatic cancer among current smokers,³² 80% prevalence of smokers among alcoholics,³³ and 30% in the Swedish general population above 18 years old in 1983,³⁴ confounding by smoking will move a true SIR of unity among alcoholics to approximately 1.4. Thus the observed excess risk in our alcoholics without complications may be almost totally attributable to the confounding effect of smoking. Even among alcoholics with chronic pancreatitis or liver cirrhosis, the excess risk is only about 100%. The confounding effect of smoking in these two cohorts may be more obvious, notably as smoking is also a risk factor for alcoholic chronic pancreatitis³⁵ or alcoholic liver cirrhosis.³⁶ There are no other conceivable confounders that would bias our results towards unity. If anything, lower socioeconomic status, lower intake of vegetables and fruits, deficiency of folate, etc, among alcoholics^{31 37 38} would bias the relative risk estimates upwards. The advantages of our study include the

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 true association.

In summary, the excess risk for pancreatic cancer among alcoholics was small, and may be totally attributable to confounding by smoking. Even among alcoholics who developed complications—that is, chronic pancreatitis or liver cirrhosis—the excess risk for pancreatic cancer was modest. Hence alcohol is unlikely to play a causal role in the aetiology of pancreatic cancer.

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Authors' affiliations

W Ye, J Lagergren, O Nyrén, H-O Adami, A Ekblom, Department of Medical Epidemiology, Karolinska Institutet, Stockholm, Sweden
E Weiderpass, Department of Medical Epidemiology, Karolinska Institutet, Stockholm, Sweden, and Unit of Field and Intervention Studies, International Agency for Research on Cancer, Lyon, France

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