Risk of pancreatic cancer after cholecystectomy: a cohort study in Sweden

W Ye, J Lagergren, O Nyrén, A Ekbom

Abstract

Background—Although some experimental studies have indicated that cholecystectomy may increase the risk of pancreatic cancer, data from epidemiological studies are conflicting.

Aims—We conducted a register based retrospective cohort study to explore the relationship between cholecystectomy and pancreatic cancer.

Subjects—The cohort included 87 263 men and 181 049 women with a documented cholecystectomy for cholelithiasis between 1965 and 1997.

Methods—By record linkage to the nationwide and virtually complete registers of Cancer, Emigration, and Causes of Death, the cohort was followed up until the occurrence of any cancer, emigration, death, or the end of follow up, 31 December 1997, whichever came first. Relative risk was estimated by standardised incidence ratio (SIR) using the Swedish nationwide sex, age, and calendar year specific cancer incidence rates as reference.

Results—During the period of observation, 1053 cases of pancreatic cancer were found, among which 231 (22%) occurred within 12 months after operation. After excluding cases and person years accrued during the first two years of follow up, we observed a non-significant 6% excess risk for pancreatic cancer (95% confidence interval (CI) –2 to 14%). The relative risk did not increase with increasing follow up duration, with a SIR equal to 0.98 (95% CI 0.79–1.20) 20 years or more after operation. Patients with a comorbidity of diabetes or chronic pancreatitis had higher relative risks (SIR=1.79, 95% CI 1.39–2.28; SIR=3.17, 95% CI 1.37–6.24, respectively). After excluding patients with recorded diabetes or chronic pancreatitis, the relative risk was close to unity (SIR=1.01, 95% CI 0.94–1.09).

Conclusions—Our findings do not support the hypothesis that cholecystectomy increases the subsequent risk of pancreatic cancer.

(Gut 2001;49:678–681)

Keywords: pancreatic cancer; cholecystectomy; cohort study

Pancreatic cancer is a highly lethal malignancy, typically presenting beyond cure.¹ Therefore, the prospect of primary prevention is appealing but little is known about its aetiology apart

from known relationships with smoking, diabetes, chronic pancreatitis, and a family history.^{2,3} Cholecystectomy has been found to increase serum levels of cholecystokinin⁴ which is a promoter in pancreatic carcinogenesis in the hamster⁵ and stimulates the growth of some human pancreatic cancer cell lines.^{6,7} Experimental studies have found that cholecystectomy may induce hypertrophy and hyperplasia in the hamster pancreas,⁸ and also predispose to pancreatic neoplasm.^{9,10} However, there are contradictory results from other studies that do not support a causal association between cholecystectomy and pancreatic cancer.^{11,12} Data from epidemiological studies are even more conflicting.^{13–25} Most studies had a case control design with obvious methodological limitations due to the extremely poor prognosis of pancreatic cancer—for example, low participation rate or the use of surrogate responders to provide exposure information. Three cohort studies have reported borderline significant excess risks of pancreatic cancer following cholecystectomy^{14,16,20} but limited statistical power due to small sample size and short follow up duration, and selection bias might explain, at least in part, these findings.

To assess the long term risk of pancreatic cancer following cholecystectomy, we conducted a large cohort study of patients who had undergone cholecystectomy in Sweden during the period 1965–1997. Our study was an update and extension of the previous study by Ekbom and colleagues¹⁶ which included data from only one health care region in Sweden (from 1965 to 1983, followed up until 1989). The present study is thus based on a considerably larger cohort with a longer follow up duration which allows for a more detailed analysis.

Methods

THE COHORT

The methodology for studies based on the Swedish Inpatient Register has been described in detail previously.^{26,27} From the register, a total of 304 815 valid and unique national registration numbers with a documented cholecystectomy from 1965 to 1997 were identified. Follow up was done through cross linkage to the registers of Causes of Deaths, Emigration, and Cancer. As the observation was censored at any first primary cancer in this analysis, we excluded 20 282 (6.7%) records with any prevalent cancer before entry. Another 6073 (2.0%) records were deleted due to

Abbreviations used in this paper: SIR, standardised incidence ratio.

Department of
Medical Epidemiology,
Karolinska Institutet,
Stockholm, Sweden

W Ye
J Lagergren
O Nyrén
A Ekbom

Department of
Surgery, Karolinska
Hospital, Stockholm,
Sweden
J Lagergren

Correspondence to:
Dr W Ye, Department of
Medical Epidemiology,
Karolinska Institutet, Box
281, SE171 77, Stockholm,
Sweden.
Weimin.Ye@mep.ki.se

Accepted for publication
29 March 2001

inconsistencies uncovered during record linkage. As cholecystectomy may be performed as a result of misinterpreted pancreatic cancer symptoms, we excluded a further 10 148 (3.3%) patients who had undergone cholecystectomy for reasons other than cholelithiasis (acute cholecystitis or obstruction of the gall bladder without calculus, unspecified diseases of the gall bladder, obstruction of the bile duct without calculus, perforation and fistula of the bile duct, other unspecified diseases of the bile duct, and pancreatitis, etc). Finally, 268 312 patients (87 263 men, 181 049 women) remained for further analysis. The cohort members were followed until a diagnosis of any cancer, death, emigration, or the end of follow up, 31 December 1997, whichever occurred first.

STATISTICAL ANALYSES

The standardised incidence ratio (SIR) together with 95% confidence interval (CI) was used as an estimate of the relative risk. In our main analyses, we disregarded cancers detected at autopsy to avoid possible ascertainment bias related to differential autopsy rates in patients with a cholecystectomy and the general population. We also excluded the person time accumulated in the first two years of follow up and pancreatic cancers detected during the same period to minimise selection bias. Such bias arises when patients with an as yet undiagnosed pancreatic cancer are more likely to be hospitalised for any ailment—for example, cholelithiasis and thus introducing a cholecystectomy—than are subjects without a concomitant subclinical cancer, and results in a spurious relationship between non-malignant events and malignancy.

Obesity may be associated with both gall stone disease²⁸ and pancreatic cancer,² and may therefore act as a confounder in the relation between cholecystectomy and pancreatic cancer. Furthermore, long term diabetes is associated with an increased risk of pancreatic cancer.²⁹ There is also an association between chronic pancreatitis and pancreatic cancer although it remains to be determined if this is causal or due to confounding such as a higher frequency of smokers in patients with chronic pancreatitis.³⁰ Diabetes or chronic pancreatitis, which will lead to an established contact with the health care system, will increase the likelihood of a cholecystectomy. We thus stratified analyses by occurrence of these comorbidities, allocating person time before the onset of comorbidities to the comorbidity negative strata. To avoid bias from the fact that preclinical stages of the outcome might affect the

probability of hospital care for these comorbidities, we disregarded data within one year before censoring. Further stratification was done by duration of follow up, age at entry, and calendar year at entry into the cohort. A χ^2 statistic was used to test any monotonic trends of SIRs.³¹

Results

Some characteristics of our cohort are shown in table 1. Mean age at operation was 53 years. Cohort members were followed up for an average of 13 years thus contributing 3 412 406 person years. Women were on average operated on at a younger age (51 *v* 57 years) and followed for a longer time (13 *v* 12 years) than men. About 1%, 6%, and 0.4% of patients with a cholecystectomy had ever been hospitalised for obesity, diabetes, and chronic pancreatitis, respectively. During the observation period, 1053 cases of pancreatic cancer were identified. Mean age at diagnosis of pancreatic cancer was 70 years.

During the first and second years of follow up, 231 (22%) and 92 (9%) pancreatic cancer cases were observed, respectively, corresponding to risks close to five times and twice that in the Swedish general population. After this peak in the first two years of follow up however we observed a minor excess risk (SIR=1.06, 95% CI 0.98–1.14) (table 2). The results were similar when we included pancreatic cancers found incidentally at autopsy in the analysis (n=769, SIR=1.07, 95% CI 1.00–1.15). The relative risk of pancreatic cancer did not vary materially with time after operation or calendar year at entry, whereas the excess risk tended to increase with decreasing age at cholecystectomy. Significant excess risks were observed among patients with concomitant diabetes (SIR=1.79, 95% CI 1.39–2.28) or chronic pancreatitis (SIR=3.17, 95% CI 1.37–6.24) (table 2). No significant excess of pancreatic cancer risk was observed in patients with both a cholecystectomy and documented obesity (SIR=1.32, 95% CI 0.53–2.73), cholecystitis (SIR=1.04, 95% CI 0.95–1.14), or additional surgery on the common bile duct (SIR=1.05, 95% CI 0.88–1.24).

After excluding patients with either diabetes or chronic pancreatitis, the relative risk of pancreatic cancer was close to unity (SIR=1.01, 95% CI 0.94–1.09). The relative risks of pancreatic cancer did not vary materially with time after operation, calendar year at entry, or age at entry. However, among cholecystectomised patients with recorded diabetes or chronic pancreatitis, relative risks tended to

Table 1. Characteristics of the cohort of patients who had a cholecystectomy for cholelithiasis, 1965–1997, Sweden

Characteristic	Men	Women	Total
No patients	87 263	181 049	268 312
Mean age at entry (y)	57.4	50.5	52.7
Mean follow up (y)	11.5	13.3	12.7
Total person years of follow up	999 434	2 412 972	3 412 406
No patients with a diagnosis of obesity (%)	571 (0.7)	3,061 (1.7)	3,632 (1.4)
No patients with a diagnosis of diabetes (%)	6 446 (7.4)	10 178 (5.6)	16 624 (6.2)
No patients with a diagnosis of chronic pancreatitis (%)	701 (0.8)	490 (0.3)	1191 (0.4)
No pancreatic cancers observed	433	620	1053
Mean age at diagnosis of pancreatic cancer (y)	70.2	69.7	69.9

Table 2 Standardised incidence ratios (SIRs) and 95% confidence intervals (CI) for pancreatic cancer among patients who had a cholecystectomy for cholelithiasis, by duration of follow up, age at entry, and calendar year at entry

	Total			With diabetes/chronic pancreatitis*			Without diabetes/chronic pancreatitis		
	Obs†	SIR	95% CI	Obs†	SIR	95% CI	Obs†	SIR	95% CI
Duration of follow up (y)									
<1	231	4.72	4.13–5.37	0	—	—	231	4.95	4.33–5.63
1	92	1.91	1.54–2.34	9	3.84	1.76–7.29	83	1.81	1.44–2.25
2–32	730	1.06	0.98–1.14	72	1.85	1.44–2.32	658	1.01	0.94–1.09
2–4	151	1.10	0.93–1.29	11	1.58	0.79–2.82	140	1.07	0.90–1.27
5–9	210	1.06	0.93–1.22	21	1.96	1.21–2.99	189	1.01	0.87–1.17
10–14	165	1.07	0.91–1.25	12	1.34	0.69–2.34	153	1.05	0.89–1.23
15–19	115	1.05	0.87–1.26	12	1.83	0.94–3.19	103	1.00	0.82–1.21
20–32	89	0.98	0.79–1.20	16	2.78	1.59–4.51	73	0.86	0.67–1.08
p value for trend‡		0.44			0.24			0.19	
Calendar year at entry§									
1965–74	352	1.10	0.99–1.22	39	2.36	1.68–3.23	313	1.03	0.92–1.15
1975–84	266	0.98	0.86–1.10	25	1.53	0.99–2.25	241	0.94	0.83–1.07
1985–97	112	1.16	0.96–1.40	8	1.31	0.56–2.58	104	1.15	0.94–1.40
p value for trend		0.91			0.05			0.67	
Age at entry (y)§									
<40	48	1.33	0.98–1.77	7	7.36	2.96–15.2	41	1.17	0.84–1.59
40–49	95	1.07	0.86–1.30	9	2.76	1.26–5.24	86	1.00	0.80–1.24
50–59	197	1.02	0.88–1.17	18	1.92	1.14–3.04	179	0.98	0.84–1.13
60–69	247	1.07	0.94–1.21	20	1.38	0.84–2.12	227	1.05	0.92–1.19
≥70	143	1.02	0.86–1.20	18	1.65	0.98–2.61	125	0.96	0.80–1.15
p value for trend		0.31			<0.01			0.60	
Diabetes§									
No	664	1.02	0.94–1.10						
Yes	66	1.79	1.39–2.28						
Chronic pancreatitis§									
No	722	1.04	0.97–1.12						
Yes	8	3.17	1.37–6.24						

*Person time before the onset of comorbidities was attributed to the comorbidity negative strata.

†Observed number of pancreatic cancer cases.

‡The category of 2–4 years after index surgery was taken as the reference.

§The first two years of observation were not included in the analyses.

increase with increasing time after operation, earlier calendar year at entry, and younger age at entry (table 2).

Discussion

We found only a 6% excess risk for pancreatic cancer in patients who had undergone a cholecystectomy for cholelithiasis 2–32 years after discharge compared with the sex, age, and calendar period matched Swedish general population. The relative risk did not increase with time after operation. Excluding patients with either diabetes or chronic pancreatitis resulted in a relative risk close to unity. Our findings do not support any important role of cholecystectomy in the carcinogenesis of pancreatic cancer, which is in line with the conclusions of most previous case control studies on cholecystectomy^{13 17–18 22–24} but in contrast with others.^{15 21 25} Selection bias may partly explain the observed excess risk as symptoms of pancreatic cancer may be misinterpreted as gall bladder disease and thus lead to a cholecystectomy.¹⁹ Not surprisingly, we found a markedly elevated risk during the first two years of follow up. In an earlier study using direct interview,²¹ an excess risk was observed for cholecystectomies performed 20 years or more before tumour diagnosis. However, other methodological limitations, including low participation rate and different recall pattern between cases and controls, may introduce selection bias or recall bias.

In cohort studies, differential misclassification of exposure (cholecystectomy) can be avoided and thus such a study design should be more appropriate for assessing the association between cholecystectomy and the risk of

pancreatic cancer. However, in the three available cohort studies reported to date, a borderline significant excess risk for pancreatic cancer was observed.^{14 16 20} Sample sizes in these studies may not have been large enough, particularly in one study in which only 13 pancreatic cancers were observed.²⁰ In our study the number of patients with a cholecystectomy was considerably larger than any previous study. Furthermore, with a longer follow up duration, person years accumulated in our study were more than four times those of the previous two register based studies.^{14 16} Another advantage of our study is that we excluded the first two year observation and patients without a recorded cholelithiasis to minimise the influence of selection bias.

Bile duct stones or manipulation during their extraction may damage the sphincter and cause continuous bile flow to the duodenum, which may reduce regurgitation of bile to the pancreatic duct. In this study however we did not confirm the previous finding that surgery on the common bile duct had a seemingly protective effect on the risk of pancreatic cancer.¹⁶ Chance is a possible explanation for the previous finding due to the limited sample size.

Despite the many advantages of our study, we should point out the limitations of register based studies. Similar to the previous two studies,^{14 16} we used the general population as our reference in which approximately 10% have prevalent cholecystectomy (in a population aged 35–85 years).³² This mixture of exposed subjects in the “unexposed” reference category leads to some underestimation of the true association. We do not have detailed information about known confounding factors but

we believe no such factor would negatively confound our findings.

In summary, in this large population based cohort study with more than three million person years at risk accumulated, we did not find evidence supporting an association between cholecystectomy and the subsequent risk of pancreatic cancer.

- 1 Carter DC. Cancer of the pancreas. *Gut* 1990;31:494-6.
- 2 Anderson KE, Potter JD, Mack TM. Pancreatic cancer. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer epidemiology and prevention*. New York: Oxford University Press, 1996:725-71.
- 3 Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. *N Engl J Med* 1993;328:1433-7.
- 4 Haddock G, Carter DC. Aetiology of pancreatic cancer. *Br J Surg* 1990;77:1159-66.
- 5 Howatson AG, Carter DC. Pancreatic carcinogenesis—enhancement by cholecystokinin in the hamster-nitrosamine model. *Br J Cancer* 1985;51:107-14.
- 6 Smith JP, Solomon TE, Bagheri S, et al. Cholecystokinin stimulates growth of human pancreatic adenocarcinoma SW-1990. *Dig Dis Sci* 1990;35:1377-84.
- 7 Axelson J, Ihse I, Hakanson R. Pancreatic cancer: the role of cholecystokinin? *Scand J Gastroenterol* 1992;27:993-8.
- 8 Rosenberg L, Duguid WP, Brown RA. Cholecystectomy stimulates hypertrophy and hyperplasia in the hamster pancreas. *J Surg Res* 1984;37:108-11.
- 9 Ura H, Makino T, Ito S, et al. Combined effects of cholecystectomy and lithocholic acid on pancreatic carcinogenesis of N-nitrosobis(2-hydroxypropyl)amine in Syrian golden hamsters. *Cancer Res* 1986;46:4782-6.
- 10 Watanapa P, Williamson RC. Experimental pancreatic hyperplasia and neoplasia: effects of dietary and surgical manipulation. *Br J Cancer* 1993;67:877-84.
- 11 Johnson FE, LaRegina MC, Martin SA, et al. Cholecystokinin inhibits pancreatic and hepatic carcinogenesis. *Cancer Detect Prev* 1983;6:389-402.
- 12 Chester JF, Norris MA, Lever JV, et al. Experimental pancreatic cancer in the Syrian hamster: effect of cholecystectomy. *Digestion* 1989;44:36-40.
- 13 Bueno de Mesquita HB, Maisonneuve P, Moerman CJ, et al. Aspects of medical history and exocrine carcinoma of the pancreas: a population-based case-control study in The Netherlands. *Int J Cancer* 1992;52:17-23.
- 14 Chow WH, Johansen C, Gridley G, et al. Gallstones, cholecystectomy and risk of cancers of the liver, biliary tract and pancreas. *Br J Cancer* 1999;79:640-4.
- 15 Cuzick J, Babiker AG. Pancreatic cancer, alcohol, diabetes mellitus and gall-bladder disease. *Int J Cancer* 1989;43:415-21.
- 16 Ekblom A, Yuen J, Karlsson BM, et al. Risk of pancreatic and periampullar cancer following cholecystectomy: a population-based cohort study. *Dig Dis Sci* 1996;41:387-91.
- 17 Friedman GD. Cholecystectomy not confirmed as a risk factor for pancreatic cancer. *Int J Cancer* 1995;61:745-6.
- 18 Gullo L, Pezzilli R, Morselli-Labate AM. Risk of pancreatic cancer associated with cholelithiasis, cholecystectomy, or gastrectomy. Italian Pancreatic Cancer Study Group. *Dig Dis Sci* 1996;41:1065-8.
- 19 Hyvarinen H, Partanen S. Association of cholecystectomy with abdominal cancers. *Hepatogastroenterology* 1987;34:280-4.
- 20 Shibata A, Mack TM, Paganini-Hill A, et al. A prospective study of pancreatic cancer in the elderly. *Int J Cancer* 1994;58:46-9.
- 21 Silverman DT, Schiffman M, Everhart J, et al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. *Br J Cancer* 1999;80:1830-7.
- 22 Mack TM, Yu MC, Hanisch R, et al. Pancreas cancer and smoking, beverage consumption, and past medical history. *J Natl Cancer Inst* 1986;76:49-60.
- 23 Jain M, Howe GR, St Louis P, et al. Coffee and alcohol as determinants of risk of pancreas cancer: a case-control study from Toronto. *Int J Cancer* 1991;47:384-9.
- 24 Farrow DC, Davis S. Risk of pancreatic cancer in relation to medical history and the use of tobacco, alcohol and coffee. *Int J Cancer* 1990;45:816-20.
- 25 Wynder EL, Mabuchi K, Maruchi N, et al. A case control study of cancer of the pancreas. *Cancer* 1973;31:641-8.
- 26 Nyren O, McLaughlin JK, Gridley G, et al. Cancer risk after hip replacement with metal implants: a population-based cohort study in Sweden. *J Natl Cancer Inst* 1995;87:28-33.
- 27 Kuper H, Ye W, Weiderpass E, et al. Alcohol and breast cancer risk: the alcoholism paradox. *Br J Cancer* 2000;83:949-51.
- 28 Diehl AK. Epidemiology and natural history of gallstone disease. *Gastroenterol Clin North Am* 1991;20:1-19.
- 29 Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. *JAMA* 1995;273:1605-9.
- 30 Karlsson BM, Ekblom A, Josefsson S, et al. The risk of pancreatic cancer following pancreatitis: an association due to confounding? *Gastroenterology* 1997;113:587-92.
- 31 Breslow NE, Day NE. *The design and analysis of cohort studies*. IARC Scientific Publications No 82. Lyon: International Agency for Research on Cancer, 1987.
- 32 Borch K, Jonsson KA, Zdzisek JM, et al. Prevalence of gallstone disease in a Swedish population sample. Relations to occupation, childbirth, health status, life style, medications, and blood lipids. *Scand J Gastroenterol* 1998;33:1219-25.

9th United European Gastroenterology Week

The UEGW abstract book (*Gut* 2001;49(suppl III)) has again been produced as a CD-ROM and can be found attached to the inside back cover of this issue.