Risk of pancreatic and periampullary cancer following cholecystectomy

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Summary

Aims: Cholecystectomy has been reported by several investigators to increase the risk of pancreatic cancer. The trophic effect on the gland by increased release of cholecystokinin following cholecystectomy and perturbation of the neurohormonal pancreatic regulation, have been suggested as possible contributing factors. However, while several investigators found that this surgical procedure increases the risk, others have not. In an attempt to clarify whether or not patients who have undergone cholecystectomy are at increased risk for developing pancreatic cancer, we evaluated the frequency with which cholelithiasis and this surgical procedure were present in a large number of patients with pancreatic cancer.

Methods: A total of 720 patients with newly diagnosed pancreatic cancer (415 men and 305 women; mean age 62.6 years, range 22 to 79 years) and 720 controls matched for sex, age, social class, and geographic region, were enrolled in the study. All subjects were interviewed personally and in detail about their clinical history.

Results: Cholelithiasis was present in 126 patients with pancreatic cancer (17.5%) and in 95 controls (13.2%), constituting a statistically significant association (odds ratio, 1.39; 95% confidence interval, 1.04 to 1.86). However, considering only the patients and controls in whom the diagnosis of cholelithiasis was made for more than one year before cancer diagnosis or interview, the association was no longer significant (odds ratio, 1.04; 95% confidence interval, 0.75 to 1.44). Cholecystectomy had been performed in 93 patients with pancreatic cancer (12.9%) and in 71 controls (9.9%). When all subjects were considered, the odds ratio was mildly, although not significantly, increased (odds ratio, 1.35; 95% confidence interval, 0.97 to 1.87). When only subjects who underwent cholecystectomy one year or more before the cancer diagnosis or interview were considered, the odds ratio fell to unity (odds ratio, 1.00; 95% confidence interval, 0.70 to 1.43).

Conclusion: This study, one of the largest on this topic, clearly shows that there is no evidence for an association between cholelithiasis, cholecystectomy, and pancreatic cancer.

Key words: cholecystectomy, pancreatic cancer, peri-ampullary cancer, risk factor

Introduction

Cholecystectomy has been reported by several investigators to increase the risk of pancreatic cancer [1-7]. The trophic effect on the pancreas by the presumed increased release of cholecystokinin following cholecystectomy and a perturbation of the neurohormonal pancreatic regulation, have been suggested as possible contributing factors [8,9]. However, while several investigators found that this surgical procedure increases the risk [1-7], many others have not [9-21]. In an attempt to clarify whether or not patients who have undergone cholecystectomy are at increased risk for developing pancreatic cancer, we recently carried out a case-control study involving a large number of patients [22].

Patients and methods

This was a case-control study, carried out in 14 Italian hospitals with experience in the management of pancreatic disease. All study subjects were patients who were hospitalized in 13 of the study centers between January 1987 and December 1989 and in the 14th center, in Bologna, between January 1987 and December 1992. We studied 720 patients (415 men and 305 women; the mean age was 62.6 years, range 22 to 79 years). The diagnosis of pancreatic cancer was based on the clinical history. It was confirmed by histologic findings in 512 of the patients (71%) and by surgery in 48 (7%); in the other 160 patients (22%), the diagnosis was confirmed by typical findings on at least three imaging procedures, as well as by the clinical course. For each patient, a control subject matched for sex, age, social class, and geographical region was selected at random from the patients hospitalized at the same time in the same hospital for acute benign disorders. All study subjects were interviewed personally about their medical history. In particular, they were asked whether they had undergone cholecystectomy and, if so, when and for what reason.

Results

Table 1 shows the prevalence of cholecystectomy in patients with pancreatic cancer and in controls, as well as the odds ratios and 95% confidence intervals. Cholecystectomy had been performed in 93 patients with pancreatic cancer (12.9%) and in 71 controls (9.9%). This had been done within 10 years from the cancer diagnosis or interview in 50 pancreatic cancer patients (53.8%) and in 32 controls (45.7%), and more than 10 years in the remaining 43 pancreatic cancer patients (46.2%) and 39 controls (54.3%). When all subjects were considered, the odds ratio was moderately, although not significantly, increased (odds ratio, 1.35; 95% confidence interval, 0.97-1.87). However,

### Table 1. Frequency of cholecystectomy in patients with pancreatic cancer and in controls, Odds Ratio (OR) and 95% Confidence Intervals (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Patients (N=720)</th>
<th>Controls (N=720)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>N %</td>
<td>N %</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>1 yr +</td>
<td>93 12.9</td>
<td>71 9.9</td>
<td>1.35 (0.97-1.87)</td>
</tr>
<tr>
<td></td>
<td>64 8.9</td>
<td>64 8.9</td>
<td>1.00 (0.70-1.43)</td>
</tr>
</tbody>
</table>

* Subjects in whom cholecystectomy was performed more than one year before cancer diagnosis or interview (Dig Dis Sci 1996; 41:1065-8)
considering only subjects who underwent cholecystectomy more than one year before the cancer diagnosis or interview, the odds ratio fell to unity.

Discussion

This study has found no evidence for an association between cholecystectomy and pancreatic cancer. When all patients and controls were considered, a small increase of risk for developing pancreatic cancer was seen, but after exclusion of those who had had a cholecystectomy performed within one year of the diagnosis of pancreatic cancer or interview, this increase was no longer present. Our results agree with those of many other authors who did not find a significant association between cholecystectomy and pancreatic cancer [9-21]. Similar to our findings, Hyvarinen and Partanen [9] noted an increased risk that disappeared after exclusion of patients with recent surgery. Their suggestion that the symptoms of pancreatic cancer may be falsely interpreted as those of gallbladder disease and that some gallbladders were operated on for the symptoms of cancer is thus supported by our data.

Other investigators, however, have reported that cholecystectomy increases the risk of developing this tumor [1-7]. While the reasons for this discrepancy are not clear, it should be pointed out that we studied a large number of patients with pancreatic cancer and conducted personal interviews; in the vast majority of other studies [1-7], the number of patients was much smaller or information was obtained indirectly from family members or questionnaires mailed to the patient’s home. Moreover, in most of these studies, the increasing risk was small and of borderline significance, and it fell below significance after exclusion of those of many other authors who did not find a significant association between cholecystectomy and pancreatic cancer [9-21]. Similar to our findings, Hyvarinen and Partanen [9] noted an increased risk that disappeared after exclusion of patients with recent surgery. Their suggestion that the symptoms of pancreatic cancer may be falsely interpreted as those of gallbladder disease and that some gallbladders were operated on for the symptoms of cancer is thus supported by our data.

Regarding the association between cholecystectomy and periampullar cancer, very few studies have been reported on this topic. In a population-based cohort study [7] consisting of 62,615 patients who had undergone cholecystectomy and were followed up for the occurrence of periampullar cancer up to 23 years, after excluding the first year after operation, there were 11 periampullar cancers vs 7.2 expected. The difference, however, was not statistically significant (SIR = 1.52; 95 % CI = 0.76-2.72).

In conclusion, I believe that it can be reasonably admitted that cholecystectomy is not a risk factor for pancreatic or periampullary cancer.

References


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