Increased Risk of Colorectal Cancer After Cholecystectomy

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The relative risk of developing colorectal cancer after cholecystectomy has been assessed in a retrospective autopsy study using controls individually matched for age and sex. Of the 304 patients dying with colorectal cancer and undergoing autopsy examination at the Helsinki University Central Hospital, 45 had undergone previous cholecystectomy. The corresponding number for the matched-pair controls without colorectal cancer was 32, indicating that the relative risk of developing colorectal cancer is slightly (1.59), but significantly ($p < 0.05$), increased after cholecystectomy. The relative risk was highest for cancer of the right colon (3.00). In contrast, no difference in the autopsy incidence of unoperated gallstones was observed between the two groups, suggesting that, rather than lithogenic bile alone, the predisposing factor is related to the cholecystectomy procedure itself.

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THE INCIDENCE OF COLORECTAL cancer is increasing in Western countries.[1,2] It has been suggested that one reason for this phenomenon is dietary habits. People eating a mixed western type of diet rich in protein and animal fat have high levels of neutral sterols and bile acids in the feces, a condition that seems to correlate with the incidence of colorectal cancer in various populations.[3-5] In particular, the quantity of secondary bile acids, *i.e.* deoxycholic acid and lithocholic acid, in the feces seems to be increased among patients with colorectal cancer,[6,7] suggesting that these agents might have a pathogenetic role in this disease. Experimental support for this proposal is provided by the finding that secondary bile acids act as tumor promoters in chemically induced colonic carcinogenesis.[8,9]

Cholecystectomy is known to increase the quantity of secondary bile acids in the enterohepatic circulation.[10,11] Therefore, if secondary bile acids do have a role in the pathogenesis of colorectal cancer one would assume that the risk for the disease is increased following cholecystectomy. Evidence to support this hypothesis had been obtained from recent clinical[12] and experimental[13] studies. In the present study, the validity of this hypothesis has been further evaluated by an analysis of autopsy material with matched-pair controls.

Materials And Methods

The autopsy material was collected from the files of the Department of Pathology, Helsinki University Central Hospital, from the years 1969–1977. All the patients during this nine-year period in whom colorectal cancer was found at autopsy examination or in whom it was closely related to death (*e.g.* removal of the tumor shortly prior to death) were included in this series. A matched-pair control for each case of colorectal cancer was selected by searching out the nearest (in time) patient who underwent autopsy examination of the same sex and age in whom no colorectal cancer was present. The autopsy records were examined thoroughly and the information concerning the gallbladder was noticed. If there was no information in the autopsy records concerning the status of the gallbladder, previous clinical records and operation notes were obtained and further information was sought.

The patients having colorectal cancer were divided into groups of cancer of the right hemicolon, the left hemicolon and the rectosigmoid. Those patients in whom the location of cancer in the transverse colon was not clearly defined by operation or autopsy records were distributed evenly between the left and right hemicolon groups. Statistical analysis of the data to estimate the relative risk of colorectal cancer was performed as described by Miettinen.[14]

Results

During the period under investigation, a total of 13,822 autopsies were performed. In 304 of the patients who underwent autopsy examination (135 males/169 females) colorectal cancer was detected.

Of the 304 patients with colorectal cancer, 45 (12 males, 33 females), or 14.8%, had undergone previous cholecystectomy. The corresponding number of the

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TABLE 1. *Incidence of Prior Cholecystectomy in Patients with Colorectal Cancer and Their Matched-Pair Controls*

Location of Cancer	No of Patients	Incidence of cholecystectomy	
		Cancer	Control
Right colon	89	14	6
Left colon	37	6	5
Rectosigmoid	178	25	21
Total	304	45	32

matched-pair controls without colorectal cancer was 32 (9 males/23 females), or 10.5%. The distribution of the cancers in the colon (right and left hemicolon and the rectosigmoid) is given in Table 1. The average time interval between cholecystectomy and the diagnosis of colorectal cancer was 11 years.

Statistical analysis of the above data indicated that the relative risk of developing colorectal cancer following cholecystectomy is significantly ($p < 0.05$) increased, 1.59, with a 90% confidence interval from 1.01 to 2.55. There was no difference in the relative risk between males (1.60) and females (1.58). The relative risk was highest for cancer of the right hemicolon (3.00), and somewhat lower, but still increased for cancer of the left hemicolon (1.20) and rectosigmoid (1.31).

The incidence of gallstones in the two groups is shown in Table 2. The number of operated gallstones was higher among patients with colorectal cancer, reflecting the higher incidence of cholecystectomy among these patients. The incidence of unoperated gallstones detected at autopsy examination was very high in both groups. However, no difference was observed between the two groups in the incidence of unoperated gallstones.

Discussion

The present results indicate that the risk of developing colorectal cancer is slightly, but significantly, increased after cholecystectomy. In particular, the risk for cancer of the right colon seems to be enhanced being three times as high as among the controls. The finding is in accordance with the data of Capron and collaborators,[12] who, likewise, demonstrated an increased incidence of prior cholecystectomy among autopsied patients with colorectal cancer as compared with nonmatched autopsy material in general, even though the difference was statistically significant only among females. In contrast, no difference was found in the present study in the incidence of nonoperated gallstones between the two groups. This suggest that, rather than lithogenic bile alone, the cause of the enhanced risk of colorectal cancer is related to the cholecystectomy procedure itself with its consequences on bile acid metabolism. The potential role of cholecystectomy as a predisposing factor in colorectal cancer is also emphasized by the experimental finding that previous cholecystectomy markedly enhances the incidence of carcinogenically (1.2-dimethylhydrazine) induced colorectal carcinoma in the mouse.[13]

TABLE 2. *Incidence of Gallstones Among Patients with Colorectal Cancer and Their Matched-Pair Controls*

Group	Number of Patients	Incidence of Gallstones	
		Removed by Cholecystectomy	Found at Autopsy Examination
Cancer	304	32	76
Control	304	18	68

Cholecystectomy is known to cause changes in the composition and kinetics of bile in man[11] and in experimental animals.[5] The size of bile acid pool remains unchanged, but the enhanced enterohepatic circulation makes the bile acid pool recycle twice as frequently as normally.[10] Furthermore, cholecystectomy markedly increases the proportion of secondary bile acids in the bile acid pool.[6,9,10] This has been explained as ensuing from the greater exposure of bile acids to intestinal bacteria, including species of Bacterioides and Clostridia which by degradiation and 7-α-dehydroxylation are capable of converting the primary bile acids to secondary bile acids.[4,16]

The carcinogenic potency of secondary bile acids has been well established in experimental models.[8,9] It has been shown that intrarectal application of the secondary bile acids, lithocholic acid and taurodeoxycholic acid, significantly increases the incidence of nitrosoguanidine-induced colorectal cancer in the rat. Futhermore, subcutaneous instillation of deoxycholic acid (which chemically resembles the carcinogenic polycyclic carbohydrates) seems to be able to directly induce sarcoma in the mouse.[7] It is possible that the increased risk of developing colorectal cancer, especially in the right hemicolon where the exposure to bile salts is highest, as demonstrated by the present study, is likewise mediated by the (co)carcinogenic influence of the secondary bile acids.

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