

Original article

## Colorectal Cancer Risk in Cholelithiasis and after Cholecystectomy in Northern Greece

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### SUMMARY

**Aim:** The aim of this study was to evaluate the possible correlation between cholelithiasis or cholecystectomy and colorectal carcinoma.

**Methods:** 400 consecutive patients with colorectal carcinoma (CRC group) were compared with 400 consecutive patients suffering from carcinoma of the breast (BC group) for the incidence of cholelithiasis and cholecystectomy.

**Results:** The group of the patients with colorectal carcinoma included 176 men and 224 women with a mean age of 60 years (24–83 years), while the group of patients with carcinoma of the breast comprised 400 women with a mean age of 55 years (25–76). The incidence of cholelithiasis and cholecystectomy was significantly higher in the CRC group (23% vs 11%,  $p < 0.01$  and 16% vs 3%,  $p < 0.001$  respectively). The elapsed time between cholecystectomy and diagnosis of malignancy was  $13.5 \pm 10.25$  years for the CRC group and  $23 \pm 15.7$  years for the BC group. No statistically significant correlation was noted concerning the incidence of cholelithiasis and gender of the patients or location of the tumor.

**Conclusion:** We conclude that the incidence of cholelithiasis or cholecystectomy is significantly higher in patients with colorectal carcinoma, implying a possible pathogenetic correlation between these two conditions. Our data showed no correlation between location of the tumor or gender of the patients and incidence of cholelithiasis.

**Key words:** cholelithiasis, cholecystectomy, colorectal carcinoma, breast cancer.

### INTRODUCTION

Cholelithiasis affects approximately 20% of the female and 10% of the male population. Although most of these patients remain asymptomatic for many years or even for a lifetime, cholecystectomy is one of the most commonly performed operative procedures. On the other hand, the wide acceptance of laparoscopic cholecystectomy may have led to the increased rate of cholecystectomies. It is estimated that more than 600.000 cholecystectomies are performed each year in the United States<sup>1</sup>.

The first clinical report relating to a possible correlation between cholecystectomy and colorectal carcinoma appeared in 1978<sup>1</sup>. Since then, more than 70 studies have been designed to confirm whether cholecystectomy could increase the risk of colon cancer with controversial or partially inconsistent results. Most of these studies report a slightly increased risk of colorectal carcinoma in cholecystectomized patients.

The proposed pathogenetic mechanisms is the increased exposure of the intestinal epithelium to secondary bile acids, which may promote carcinogenesis as was indicated shown in several clinical and experimental studies<sup>2,3</sup>. However, whether this possible correlation should lead to screening of the cholecystectomized patients for colorectal cancer remains questionable.

The aim of this study was to evaluate the possible correlation between cholelithiasis or cholecystectomy and colorectal carcinoma.

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## PATIENTS – METHODS

We retrospectively evaluated the charts of 400 consecutive patients with colorectal carcinoma, who were treated in our hospital in the period 1990-2000. These data were compared with 400 consecutive patients suffering from carcinoma of the breast, who were treated in our hospitals during the same period.

The following parameters were recorded: age and gender of the patient, location of the tumor, presence of cholelithiasis at the time of diagnosis of the malignancy, history of cholecystectomy, elapsed time between cholecystectomy and diagnosis of malignancy. The diagnosis of cholelithiasis was based on the medical history of the patients (e.g. history of cholecystectomy, biliary colic), and confirmed with ultrasonography of the upper abdomen. In asymptomatic patients, cholelithiasis was an incidental finding in US or CT, which was performed in all cases during the preoperative staging of the tumor.

Data are expressed as the mean  $\pm$  SD. Parametric data were compared between groups by analysis of variances (ANOVA) and post-hoc testing. Statistical significance was assumed, if  $p < 0.05$ . Non-parametric data were analysed using chi-square tests between groups. Analysis was performed with the Statistical Package for the Social Sciences (SPSS, Inc., Chicago IL).

## RESULTS

The group of patients with colorectal carcinoma

(CRC) included 176 men and 224 women with a mean age of 60 years (24–83 years), while the group of patients with carcinoma of the breast (BC) comprised 400 women with a mean age of 55 years (25–76).

The incidence of cholelithiasis at the time of diagnosis of the carcinoma was significantly higher in the CRC group compared to the BC group (92/400, 23% vs 44/400, 11%;  $p < 0.01$ ). The incidence of cholecystectomy was also significantly higher in the CRC group (64/400, 16% vs 12/400, 3%;  $p < 0.001$ ).

The elapsed time between cholecystectomy and diagnosis of malignancy was  $13.5 \pm 10.25$  years for the CRC group and  $23 \pm 15.7$  years for the BC group (Table 1). No statistically significant difference was noted between men and women with colorectal carcinoma concerning the incidence of cholelithiasis (32/152, 21.1% vs 60/248, 24.2%;  $p = \text{n.s.}$ ) or cholecystectomy (20/152, 13.2% vs 44/248, 17.7%;  $p = \text{n.s.}$ ) (Table 2). No statistical correlation was recorded between location of the colorectal tumor and incidence of cholelithiasis or cholecystectomy. The incidence of cholelithiasis for tumours located in the right and left colon was 16.6% and 21% respectively ( $p = \text{n.s.}$ ). The incidence of cholecystectomy also showed no significant difference between left and right colon (16.6% vs 17%) (Table 2).

## DISCUSSION

The biology of colorectal cancer has been thoroughly

**Table 1.** Demographic characteristics and incidence of gallstone disease and cholecystectomy in patients with colorectal carcinoma (CRC-group) and breast carcinoma (BC-group)

	CRC-group (n=400)	BC-group (n=400)
Gender (female:male)	224:176	400:0
Mean age	60 years (24–83)	55 years (25–76)
Cholelithiasis	92/400 (23%)*	44/400 (11%)*
History of cholecystectomy	64/400 (16%)+	12/400 (3%)+
Elapsed time from cholecystectomy	$13.5 \pm 10.25$ years	$23 \pm 15.7$

\* $p < 0.001$ , + $p < 0.001$

**Table 2.** Incidence of cholelithiasis and cholecystectomy according to gender and location of the colon cancer

	Cholelithiasis	History of cholecystectomy
Men (n=152)	32/152 (21.2%)	20/152 (13.2%)
Women (n=248)	60/248 (24.2%)	44/248 (17.7%)
Proximal colon (n=144)	24/144 (16.6%)	24/144 (16.6%)
Distal colon (n=256)	54/256 (21.1%)	44/256 (17.2%)

studied in recent decades. Although research has mainly focused on the hereditary aspects of this malignancy, the effect of certain environmental factors (e.g. diet, external carcinogens) has also been extensively investigated.

The relation between cholelithiasis, cholecystectomy and colorectal cancer has been controversial. A possible etiologic relation of these conditions could be of great clinical importance, since cholecystectomy is one of the most commonly performed operations. The introduction of laparoscopic surgery has led to an increase in the number of cholecystectomies performed worldwide. A reasonable concern would be if this increase in the number of performed cholecystectomies had led to an increased incidence of colorectal cancer. A further consideration relating to the performance of laparoscopic cholecystectomy is the reported increased incidence of missed pathology of other intraperitoneal organs during laparoscopy. It seems, however, that this risk is no higher than with open cholecystectomy, if certain safety rules are followed<sup>2,3</sup>.

The suggested association between gallstones and colon cancer is biologically plausible. Patients with gallstones have increased biliary and fecal concentrations of secondary bile salts<sup>4</sup>. Cholecystectomy leads to an even more increased concentration of primary bile acids in the intestinal lumen, which are transformed through intestinal bacteria to secondary bile salts<sup>5</sup>. The role of secondary bile acids as an endogenous colon carcinoma has been shown in a number of clinical and experimental studies<sup>6,7</sup>. Narisawa et al proved that secondary bile salts can promote colonic epithelial cell proliferation in animal models<sup>8</sup>.

Further clinical evidence on the association between cholecystectomy and colon cancer was supplied by Mannes et al, who reported a significantly increased incidence of large bowel adenomas after cholecystectomy, especially in the subgroup of patients aged 60–80 years with a postcholecystectomy interval of more than 10 years<sup>9</sup>. These results correlate with the observation that the mitotic index of the colonic mucosa is significantly increased after cholecystectomy<sup>10</sup>.

On the other hand, cholelithiasis and colon cancer have a similar geographic distribution and share common dietary and chemical pathogenetic factors. It is known, for example, that the risk for colon cancer is increased with a diet rich in fat, as is the risk for the development of gallstones. These observations have led many authors to the assumption that the association between gallstones and colon cancer could be simply explained through the

existence of common risk factors<sup>7,11,12</sup>.

The most reliable evidence was supplied by large follow-up studies of cholecystectomized patients. In 1993 Giovanucci<sup>13</sup> performed a meta-analysis of the existing data in the literature showing a slightly increased relative risk for colorectal cancer after cholecystectomy (1.21 for men and 1.24 for women) (data from 38 cohort and case-control studies). Furthermore, he noted an increased risk for proximal cancer overall (pooled RR 1.88) (data from 33 studies). Finally, 6 of 7 autopsy studies and the 9 prevalence studies with no external controls showed that the ratio of proximal to distal colorectal tumors was increased in patients who had previous cholecystectomies.

Since this report, three more large cohort studies have been published in the literature. Ekblom et al (62,615 patients, follow-up <23 years) reported no increased risk of colorectal cancer following cholecystectomy. However, he observed an increased risk among women for right-sided colon cancer 15 years after the operation (14). Johansen et al (42,098 patients, follow-up <15 years) showed only a borderline significant association between cholelithiasis and colon cancer<sup>15</sup>. Lagergren et al (278,460 patients, follow-up <33 years) concluded that cholecystectomized patients had an increased risk of proximal intestinal adenocarcinoma, which gradually declined with increasing distance from the common bile duct<sup>16</sup>.

Concerning the question whether cholecystectomized patients should be put on a screening programme for early detection of colon cancer, almost all authors agree that there is no evidence to suggest the need for increased surveillance for colon cancer in individuals after cholecystectomy<sup>17-21</sup>.

Our data showed that the incidence of cholelithiasis and cholecystectomy were significantly higher in patients with colorectal carcinoma compared with patients with breast carcinoma (23% vs 11%;  $p < 0.01$  and 16% vs 3%;  $p < 0.001$  respectively). Although the patients with colorectal cancer were older than those with breast cancer, this fact cannot explain the great difference in the incidence of cholelithiasis and cholecystectomy between the two groups. On the other hand, the incidence of cholelithiasis and cholecystectomy among women with colon cancer was significantly higher than in women with BC. Furthermore, the incidence of cholelithiasis and cholecystectomy among men with colorectal carcinoma was significantly above the expected incidence for their age (21.1%). The mean elapsed time between cholecystectomy and diagnosis of colon cancer was 13.5 years. Nearly all studies showing an association between

cholecystectomy and colon cancer suggest that the risk persists or increases over time. Continued elevation or risk beyond an interval of 10-15 yrs is also biologically plausible in view of the adenoma-carcinoma sequence and the limited data that the incidence of colonic adenomas is increased after cholecystectomy<sup>9,22</sup>. However, our study did not show any significant association between location of colorectal tumor, gender of the patient and presence of cholelithiasis or history of cholecystectomy.

In conclusion, we observed a significantly increased incidence of gallstones and cholecystectomy among patients with colorectal carcinoma compared with patients with breast cancer. However, since the exact pathogenetic association of these conditions has not been fully proved and explained, there is no need for increased surveillance of these patients.

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