Cholecystectomy and adenomatous polyps of the large bowel

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SUMMARY   Seventy two patients (39 women) with colonic adenomas were compared with 72 adenoma free controls (39 women) to investigate the possible association between previous cholecystectomy and the subsequent development of adenomas. Data were gathered retrospectively from medical records. Overall there was no significant association between colonic adenomas and previous cholecystectomy. When women are considered separately, however, eight cases and no controls had undergone cholecystectomy (odds ratio∞lower 95% confidence limits 1·7, p>0·01). No association between previous cholecystectomy and large bowel adenomas was found in men. Four of nine (44·4%) women with right sided colonic adenomas had undergone previous cholecystectomy compared with only three of 23 (13%) women with left sided adenomas.

Several recent studies[1-6] have investigated the relationship between colonic cancer and previous cholecystectomy. Most have indicated an increased risk for women of developing right sided colonic cancer after cholecystectomy,[1 2 4 5] but at least one study has shown a stronger association with rectal cancer,[3] and some investigators have been unable to confirm any relationship.[6]

As colonic adenomatous polyps are generally thought to be precursors of colonic carcinoma,[7-9] the purpose of this study was to determine whether there was any association between the presence of such lesions and previous cholecystectomy.

Methods

PATIENTS
The study population consisted of patients who underwent diagnostic colonoscopy during the years 1980 to 1982 in the Royal Brisbane Hospital, Department of Gastroenterology. There were 72 cases (39 women) for whom a matched control could be found. The patients were aged 30–85 years, in whom one or more colonic or rectal polyps were

detected on colonoscopy, and who had no evidence of present or past large bowel cancer. The control group consisted of 72 men and women, in whom colonoscopy was normal, individually matched for age (±5 years) and sex.

The controls were selected consecutively from a colonoscopic diagnostic listing as having had a normal colonoscopy, with no past history of adenoma, colonic cancer, or other disease of the large bowel.

The proportions of patients excluded, because their charts were unavailable or contained insufficient data to determine cholecystectomy status, were comparable in the two groups (22·8% adenoma patients and 29·4% controls).

Data were obtained by retrospective review of medical records and colonoscopy reports of adenoma and control patients, and were recorded on standard forms. Cholecystectomy status was determined by review of the past history and clinical examination sections of the medical records, as well as the surgeon's operation reports. Other gastrointestinal surgery, as well as the presence or absence of gall stones was also recorded. Histological type, size, number, and site of adenomas were noted from pathology and colonoscopy reports. Standard case control analyses (matched or unmatched as appropriate) were carried out using computation of odds ratio, 95% confidence limits and exact tests.[10]

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Results

The average age at colonoscopy of adenoma patients was 57·3 years, and of controls was 55·6 years. Histological information was available in 54·2% of cases, the majority of adenomas being tubular or tubulovillous (Table 1). Thirty eight (52·8%) of the patients had only a single adenoma, 32 (44·4%) had between two and six adenomas, and two had more than six. The distribution of adenomas in the colon is shown in Table 2. Forty four (61·1%) of the

Table 1   *Histological classification*

Histological type	Patients (%)	Patients (n)
Villous adenoma	1·4	1
Tubulovillous adenoma	18·1	13
Tubular adenoma	34·7	25
No histology available	45·8	33
Total	100·0	72

Table 2   *Distribution of adenomas in colon*

Site	Patients (%)	Patients (n)
Caecum	9·7	7
Ascending colon	2·8	2
Hepatic flexure	0·0	0
Transverse colon	13·9	10
Splenic flexure	2·8	2
Descending colon	11·1	8
Sigmoid colon	66·7	48
Rectum	23·6	17

NB: Percentage total exceeds 100% because some patients had adenomas in several sites.

adenomas were less than 11 mm in diameter, eleven (15·3%) were between 11 and 30 mm and two (2·8%) were greater than 30 mm. No measurements were available in 15 (20·8%).

The matched pair analysis of cholecystectomy status is shown in Table 3. Overall, the proportion of adenoma patients having had a previous cholecystectomy was 11·1% (8/72) compared with 2·8% (2/72) for controls. When the sexes are considered separately, however, some interesting differences emerge. Very few men had a history of cholecystectomy, and the 95% confidence interval for the odds ratio is, in consequence wide (0·0–5·3). On the other hand, none of the 39 women controls had a history of cholecystectomy compared with eight of 39 women with adenomas (lower 95% confidence bound 1·7 (p<0·01); matched analysis). The average time interval between cholecystectomy and colonoscopic diagnosis of adenomas in women was 4·5 years, range 7 months to 11 years.

Patients with adenomas in the caecum, ascending colon, hepatic flexure and/or transverse colon were classed as 'right sided adenoma patients', while those with adenomas in the splenic flexure, descending colon, sigmoid colon and/or rectum were classed as 'left sided adenoma patients'. The distribution in regard to cholecystectomy status in female patients is shown in Table 4. Of women with right sided adenomas, 44% had undergone cholecystectomy, in contrast with only 12% of those with left sided lesions (odds ratio 6·13, 95% confidence limit 0·7–53·1, p=0·11). Patients with adenomas on both sides of the colon were excluded from this analysis.

There were no associations of polyps with a variety of types of previous gastrointestinal surgery

Table 3   *History of cholecystectomy in adenoma and control patients (matched analysis)*

		Adenoma Patients			
		Positive	Negative	Total	95% Confidence limits for odds ratio
1. Men					
Controls	Positive	0	2	2	
	Negative	0	31	31	
	Total	0	33	33	
2. Women					
Controls	Positive	0	0	0	
	Negative	8	31	39	
	Total	8	31	39	
3. Men and women					
Controls	Positive	0	2	2	
	Negative	8	62	70	(0·8–38·7)
	Total	8	64	72	

Note: 'Positive' and 'negative' refer to history of cholecystectomy.

Table 4 *Distribution of adenomas in female patients*

	Previous cholecystectomy		
Group	Yes	No	Total
Right sided adenomas	4	5	9
Left sided adenomas	3	23	26
Totals	7	28	35*

*Four female patients with adenomas both sides are excluded from this Table.

(including appendicectomy, hernia repair, vago-
tomy, and surgery for inflammatory bowel disease).

Discussion

The results of this study suggest that cholecystec-
tomy increases subsequent risk of developing adeno-
mas of the large bowel in women, a finding which is
congruent with increasing evidence of an association
between previous cholecystectomy and the develop-
ment of large bowel cancer.[1-5] The data also suggest
a tendency for adenomas to occur on the right side
of the colon after cholecystectomy in women paral-
leling a similar right sided preponderance found for
colon cancer after cholecystectomy.[5] Vernick et al[4]
argue that the right side of the colon is most likely to
be affected by the potential carcinogenic effect of
bile salt metabolites.

The lack of any apparent association between
cholecystectomy and the development of adenomas
in men in this study may merely be because of their
relative infrequency of cholecystectomy, but is also
consistent with the sex distribution found in some
studies of large bowel cancer.[1 2] As such, it might
reflect sex differences in bowel function, such as
slower bowel transit time in women,[11] or that
women have a higher proportion of secondary bile
acids in their bile than men.[12]

These results are consistent with bile salt/bacterial
theory of the aetiology of colorectal cancer pro-
posed by Hill, Drasar, and Williams.[13] Cholecystec-
tomy could predispose to the development of polyps
of the large bowel and to cancer, by virtue of its
effect on bile salt pool dynamics. Werner and de
Heer[14] have shown that cholecystectomy promotes
colonic carcinogenesis induced by 1,2-dimethyl hyd-
razine (DMH) in rats (although others have not
reproduced this finding[15]). Cholecystectomy alters
bile salt metabolism, and increases exposure of
primary bile salts to colonic bacteria, thereby in-
creasing the production of secondary bile salts,[16-18]
which have been implicated as colorectal carci-
nogens. They are found in raised concentrations in

faecal specimens from subjects living in countries
with a high incidence of colonic cancer.[13] In a case
control study,[19] faecal concentrations of secondary
bile salts were higher in patients with colon cancer
and in patients with adenomatous polyps of the
colon, than in patients with other digestive diseases
and in normal controls; and laboratory studies[20 21]
have shown that the secondary bile acids, lithocholic
acid, and deoxycholic acid, act as cocarcinogens in
experimentally induced colonic cancer in animals.

Although the bile salt/bacterial theory of mechan-
ism of development of colonic cancer and adenomas
is an attractive one, there are several other explana-
tions for the apparent association between previous
cholecystectomy and development of colonic adeno-
mas. Gall bladder disease itself, and not cholecys-
tectomy *per se*, could lead to increased risk of
cholecystectomy and of colonic adenomas and can-
cer. A recent study has examined the relationship
between cholecystectomy, silent cholelithiasis and
colonic adenomas. Mannes et al[22] compared the
prevalence of adenomatous polyps detected at
colonoscopy in 333 patients who had previously
undergone cholecystectomy with an asymptomatic
group of 406 patients shown by ultrasonography to
have gall stones in the gall bladder. There were no
differences between these groups except among
those aged 60–80 years. Patients who had undergone
a cholecystectomy more than 10 years ago had
significantly more adenomas (38·5%) (and cancers)
than either those having had their cholecystectomy
less than 10 years ago (21·8%) or a matched
cholelithiasis group (23·7%). These results suggest
that in the short term, cholecystectomy does not
increase the rate of development of adenomas or
cancers among those with gall bladder disease, but
longer derangement of bile acid circulation may
increase this risk among elderly patients. Additional
support for a role for gall bladder disease *per se*
comes from other research,[23] which suggests that it
is patients with gall stones, and not specifically those
undergoing cholecystectomy, who have increased
proportions of secondary bile acids. Findings in this
area, however, are contradictory.[17 23 24] Furth-
ermore, although gall stones are much more com-
mon in women[25] the sex difference in patients with
colorectal cancer is only modest.[3 26] On the other
hand, it might be that previous gastrointestinal
surgery somehow increases the risk of developing
colonic adenomas and cancer. This seems unlikely,
as previous work[27 28] has shown no increased risk of
colonic cancer with various surgical procedures, and
our data show no relationship with any procedure
other than cholecystectomy.

Finally, in evaluating the validity of our findings,
methodological weaknesses and possible sources of

bias should be considered. Although the sample size is small, chance appears to be an unlikely explanation of the results among women. It is possible that biases associated with retrospective review of hospital records could produce a spurious association between previous cholecystectomy and development of large bowel polyps. The higher cholecystectomy prevalence in a population sample of women of similar age to our own controls (11·6% compared with 0%, unpublished observation, Bain 1983), suggests that there may well have been some selection bias. Even using the higher estimate, however, female adenoma patients in this study remain approximately twice as likely as the general population to have had a cholecystectomy. Undertaking colonoscopy on all patients ensured accurate ascertainment of adenoma status, and the use of standard abstraction forms and procedures makes bias with respect to noting past cholecystectomy unlikely. Further, assuming any misclassification of cholecystectomy status is random could only mean that the real association is stronger than that observed. Moreover, the fact that such a relationship is consistent with the growing body of evidence that supports the bile salt/bacterial theory of development of colonic neoplasms makes it less likely that these findings are spurious.

In conclusion, the present study suggests that cholecystectomy may be a predisposing factor in the development of adenomas of the large bowel in women, particularly of the right colon. A larger study involving interview of patients at the time of colonoscopy is in progress in an attempt to investigate this issue further.

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