Null Results in Brief

Cholecystectomy and the Risk of Recurrent Colorectal Adenomas

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Abstract

Prior studies have shown an increased risk of colorectal cancer following cholecystectomy, but few studies have explored the association between cholecystectomy and the risk of colorectal adenomas. We used data from three large randomized adenoma chemoprevention trials to explore the association between cholecystectomy and the occurrence of adenomas. After adjusting for confounding factors, we found no increased risk for adenomas among individuals who had undergone cholecystectomy [risk ratio (RR), 1.02; 95% confidence interval (95% CI), 0.88-1.18]. There was a slight increase in the risk of advanced recurrent adenomas (RR, 1.28; 95% CI, 0.94-1.76) and multiple advanced recurrent adenomas (RR, 1.34; 95% CI, 0.97-1.85) but the 95% CIs included the null in both cases. We conclude that the increased risk for colorectal cancer following cholecystectomy seems to be due to a biological process occurring after the adenoma has developed. (Cancer Epidemiol Biomarkers Prev 2007;16(7):1523–5)

Introduction

Individual studies of the effects of cholecystectomy on the risk of colorectal cancer, as well as two large meta-analyses, have shown an increase in the risk of colorectal cancer following cholecystectomy (1-6). The association between cholecystectomy and adenomas, the precursor to colorectal cancer, has been less studied. Most studies with adenoma end points had small sample sizes and did not report effect measure modifiers or confounding factors (2).

The increased risk of colorectal cancer following cholecystectomy could be due to either an increased risk of adenomas or an accelerated transition from adenoma to cancer. If prior cholecystectomy increased the risk for subsequent adenoma formation, this could have practical implications for the recommended surveillance intervals for these patients, and could increase our understanding of the etiology of colorectal carcinogenesis. In order to examine the relationship between cholecystectomy and colorectal adenomas, we analyzed data from three large colorectal adenoma prevention trials.

Materials and Methods

We used data from the Antioxidant Polyp Prevention Study, the Calcium Polyp Prevention Study, and the Aspirin/Folate Polyp Prevention Study, which are described elsewhere (7-9). In brief, all participants had a colonoscopy removing all polyps shortly before study entry. Medical history was assessed at baseline using questionnaires. Self-response questionnaires regarding lifestyle, diet, and medical events were completed every 6 months in the Calcium Polyp Prevention Study and every 4 months in the two other studies. The timing of subsequent surveillance colonoscopy also varied by trial, occurring 1 and 4 years after enrollment in the Antioxidant and Calcium Polyp Prevention Studies and only 3 years after enrollment in the Aspirin/Folate Polyp Prevention Study.

The main outcome of interest for this analysis was recurrent adenoma during the treatment period. Any individual with one or more adenomas detected after the baseline clearing colonoscopy satisfied this outcome measure. History of cholecystectomy was based on the subjects' self-report which was obtained at study entry. Covariates examined as potential effect measure modifiers (using a test of homogeneity and an a priori cutoff of $P \leq 0.15$) or confounders [using the criteria for confounding (10) and the change-in-estimate approach] were sex (male, female), age (continuous), body mass index (continuous), history of a first-degree relative with colorectal cancer (yes, no), smoking status (current, past, never), lifetime number of adenomas at the start of the study (continuous), and treatment group in the trial (nominal categorical). We used a log-linear binomial regression model to evaluate the association between cholecystectomy and colorectal adenomas. Subsequent analyses assessed the association between cholecystectomy and risk of advanced adenoma (adenomas with diameter of at least 1 cm, with at least 25% villous component, or with advanced dysplasia or invasive cancer), multiple adenomas (three or more adenomas detected during all follow-up visits combined), and multiple advanced adenomas (more than one advanced adenoma detected during the follow-up visits). We also examined whether the risk of adenomas increased with time since cholecystectomy. Based on prior findings (11, 12), this was dichotomized as at least 10 years prior and less than 10 years prior to study entrance.

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Table 1. Characteristics of participants who did/did not undergo cholecystectomy (Polyp Prevention Studies)

	Cholecystectomy (n = 212)	No cholecystectomy (n = 2,388)
Colorectal adenomas at any follow-up (%)	102 (48.11)	1,135 (47.53)
Sex—men (%)	90 (42.45)	1,734 (72.61)
Smoking status (%)		
Never	103 (48.58)	872 (36.52)
Former	77 (36.32)	1,093 (45.77)
Current smoker	31 (14.62)	405 (16.96)
Missing	1 (0.47)	18 (0.75)
Age, y (%)		
<50	20 (9.43)	330 (13.82)
50-59	53 (25.00)	811 (33.96)
60-69	105 (49.53)	927 (38.82)
≥70	34 (16.04)	320 (13.40)
Mean age (SD)	61.88 (8.81)	59.20 (9.18)
Body mass index		
<25.0	53 (25.00)	743 (31.11)
25.0-29.9	81 (38.21)	1,127 (47.19)
≥30	78 (36.79)	518 (21.69)
Mean body mass index (SD)	28.68 (5.43)	27.18 (4.24)
Family history of colon cancer (%)	49 (23.11)	606 (25.38)
Lifetime number of adenomas at intake (%)*		
1	94 (44.34)	1,078 (45.14)
2	44 (20.75)	547 (22.91)
3	31 (14.62)	320 (13.40)
4	17 (8.02)	165 (6.91)
5+	26 (12.26)	278 (11.64)
Mean no. of adenomas (SD)	2.55 (2.62)	2.42 (2.51)

*Percentage among those with colorectal adenoma at follow-up.

Results

Nearly all of the randomized subjects in the trials completed a follow-up colonoscopy (97.8%). In all, 2,600 study participants completed both at least one follow-up colonoscopy and provided complete information on the exposure and covariates included in the model. The majority of study participants were men; however, most participants who had undergone a cholecystectomy were women (Table 1).

The final regression model was adjusted for age and sex, the covariates found to confound the association. No variables met the criteria of an effect measure modifier. The risk ratios and 95% confidence intervals for those who had a cholecystectomy prior to study enrollment compared with those who had not was 1.02 (0.88-1.18; Table 2). The risk ratio was 0.99 (0.82-1.21) for men and 1.06 (0.85-1.33) for women. Additional analyses found no association between cholecystectomy and the risk of multiple adenomas (Table 2). The risk of advanced adenomas and the risk of multiple advanced adenomas were slightly increased but did not reach statistical significance (Table 2).

Compared with those without cholecystectomy, the risk ratio (95% confidence interval) for cholecystectomy less than 10 years prior to study entry was 1.18 (0.97-1.44) and was 0.93 (0.76-1.13) for cholecystectomy at least 10 years prior to entrance into the study (Table 2).

Discussion

Using data from three colorectal adenoma chemoprevention trials, we did not find any association between prior cholecystectomy (or time since cholecystectomy) and recurrent colorectal adenoma formation. The lack of association was apparent for both men and women.

In contrast, a few previous studies have shown an association between cholecystectomy and risk of colorectal adenomas, although only among women (4, 13, 14). Other studies found no association at all (5, 15, 16). Our analysis also explored the risk of multiple and advanced recurrent adenomas, end points that probably have more relevance for risk of invasive cancer than single small tubular adenomas. There was no increased risk for multiple recurrent adenomas; however, the risks for advanced and multiple advanced recurrent adenomas were slightly (but not statistically significantly) increased among subjects with a history of cholecystectomy.

A decided strength of this study was the large size with 2,600 participants in the pooled analysis. Follow-up was nearly complete and every patient in the analysis underwent a complete colonoscopy to enumerate adenomas that had developed after randomization. Nonetheless, some of the adenomas that we observed could have been missed at baseline rather than truly incident. This would bias the study toward the null. One further limitation is that the information

Table 2. Association between colorectal adenomas and cholecystectomy

	Adenoma at any follow-up (n)	No adenoma at any follow-up (n)	Risk ratio (95% confidence interval)*
No cholecystectomy	1,135	1,253	1.00
Cholecystectomy	102	110	1.02 (0.88-1.18)
<10 y prior	42	33	1.18 (0.97-1.44)
≥10 y prior	60	77	0.93 (0.76-1.13)
	Advanced adenoma at any follow-up (n)	**No advanced adenoma at any follow-up (n)**	**Risk ratio (95% confidence interval)***
No cholecystectomy	324	2,080	1.00
Cholecystectomy	35	176	1.28 (0.94-1.76)
	≥3 Adenomas at any follow-up (n)	**<3 Adenomas at any follow-up (n)**	**Risk ratio (95% confidence interval)***
No cholecystectomy	68	2,320	1.00
Cholecystectomy	7	205	1.08 (0.50-2.35)
	>1 Advanced adenoma at any follow-up (n)	**≤1 Advanced adenoma at any follow-up (n)**	**Risk ratio (95% confidence interval)***
No cholecystectomy	294	2,092	1.00
Cholecystectomy	35	177	1.34 (0.97-1.85)

*Adjusted for age and sex.

about cholecystectomy was by self-report and was not validated. Finally, all our subjects had at least one lifetime adenoma; we could only assess risk of recurrence.

In conclusion, there does not seem to be an association between cholecystectomy and recurrent colorectal adenomas. If cholecystectomy increases the risk of colorectal cancer, these results would suggest that cholecystectomy influences the adenoma to cancer transition and not adenoma formation itself. As such, patients with prior cholecystectomy are not at increased risk for adenomas and require no special follow-up.

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