E. Kyriacou¹, R. Knill-Jones²

The Role of Previous Cholecystectomy in Patients with Colorectal Cancer
A Meta-Analysis and Review

Summary. There is a large body of literature which undertakes to look at a possible association between cholecystectomy and colorectal cancer. We set out to conduct a meta-analysis to investigate this. The overall odds ratio for all studies looked at was 1.36 with 95% confidence intervals (CI) 1.07 to 1.74, significant at the 5% level (p = 0.014). The overall odds ratio for a subset of studies deemed “good studies” established by a customised ranking score was 1.66 (1.34 to 2.03), p < 0.0001. The odds ratios for cohort and necropsy studies were also ascertained and discussed. Our results would tend to support the above hypothesis. However, the limitations of this review are also discussed, and finally we suggest that if such an association is indeed real then the increased risk is likely to be small.

(Key Words: Colorectal cancer · Cholecystectomy · Secondary bile acids · Meta-analysis)

Die Rolle einer früheren Cholezystektomie bei Patienten mit kolorektalem Karzinom.
Zwischenanalyse und Übersicht

Zusammenfassung. Es existiert zahlreiche Literatur über einen möglichen Zusammenhang von Cholezystektomie und kolorektalem Karzinom. Wir initiierten deshalb eine Metaanalyse, um diese Möglichkeit zu überprüfen. Das gesamte Wahrscheinlichkeitsverhältnis aller ausgewerteten Untersuchungen lag bei 1,36 mit einem Vertrauensintervall von 95% (1.07 bis 1.74); Signifikanz war bei 5% gegeben (p = 0.014). Das gesamte Wahrscheinlichkeitsverhältnis für einen Teil der Untersuchungen, die als „gute Untersuchungen“ anzusehen waren und für die ein einheitliches Bewertungssystem vorlag, betrug 1,66 (1.34 bis 2.03, p = 0,0001). Das Wahrscheinlichkeitsverhältnis für Sammel- und Autopsiestudien wurde ebenfalls überprüft und diskutiert. Unsere Ergebnisse unterstützen die vorgenannte Hypothese. Allerdings werden auch die Grenzen dieser Übersicht diskutiert, wobei wir schlussfolgernd davon ausgehen, daß eine solche Assoziation vorläufig nicht klar sein kann, falls sie tatsächlich existiert.

(Schlüsselwörter: Kolorektales Karzinom · Cholezystektomie · Sekundäre Gallensäure · Metaanalyse)

It is unknown whether altered bile salt metabolism increases colonic cancer after cholecystectomy or whether the 2 conditions share common aetiological factors [5]. Since both colorectal carcinoma [16, 41] and cholelithiasis are common and are important causes of mortality or morbidity respectively, then it is of interest to know whether they occur together more often than expected by chance.

The proposed aetiology of this link is related to alterations in the bile salt pool following cholecystectomy. Cholecystectomy exposes the gut to bile continuously rather than intermittently after feeding which allows
increased enterohepatic circulation and degradation of primary bile acids by bacteria [66]. Many strains of colonic anaerobes can dehydrogenate the 7-alpha hydroxyl group of bile acids, converting cholic acid to deoxycholic acid, and chenodeoxycholic acid to lithocholic acid [56]. Bile acid measurements in some studies have indicated increased conversion of primary to secondary bile acids following cholecystectomy, whilst other studies have not shown this increase in secondary bile acids [6, 19, 25, 28, 30–34, 41, 50, 56, 66], even up to 8 years following cholecystectomy [39, 77]. Secondary bile acids can act as co-carcinogens in chemically induced cancer of the colon in rats [67], and also in cholecystectomised mice [56, 83], although not all mouse experiments universally support this view [70]. These co-carcinogens may play a role in the development of colorectal cancer in man, and it is important to establish whether there is epidemiological evidence of an association in man.

Patients and Method

A 20-year Medline search was carried out from 1975 to 1995, using the key words: cholecystectomy and colorectal cancer in the title, for all English language articles only. Articles mentioning only cholelithiasis rather than cholecystectomy were excluded from the study as were articles concerned with the development of colonic polyps or adenomas rather than frank colorectal carcinoma, as well as articles from journals only obtainable from non UK libraries. Citations from the original articles from Medline were obtained if thought to be relevant from their title, thus extending the search results. Citations from these references were also obtained if relevant. The results were also double checked by searching the EMBASE database using the University BIDS (Bath Information and Data Services) link facility, in order to pick up any additional references. The BIDS EMBASE Service at Bath University provides computer access to the Excerpta Medica database covering 3,300 journals and covers pharmacological and biomedical literature. The data is supplied by Elsevier Science publishers B. V. Amsterdam. Edinburgh University is a subscribing organisation. Articles whose raw data was too ambiguous to be extracted and used in the analysis were excluded early on. The studies for inclusion in the meta-analysis were ranked in order to establish a more highly ranked subset, defined in terms of the numbers of subjects, quality and choice of controls – such as age, sex matching and randomisation, and also to pick out and analyse results separately for the cohort studies and necropsy studies. This procedure of ranking the component studies was used as a test of the robustness (sensitivity analysis) of the overall results. Criteria for ranking in the sensitivity analysis were as follows:

Sensitivity Analysis

Minus 10 points were awarded to any study with unclear raw data (leading to automatic exclusion from the study). All remaining studies were included for ranking and scored. The more highly ranked studies were also called “good studies” for the sake of brevity. They were those studies gaining 5 or more points up to a maximum of 19 points, as follows:

0 to 1 points (maximum of 5) for:
- Study size small or large (cut-off 50 cases),
- suitability of controls,
- matching for age present,
- matching for sex present,
- randomisation.

0, 1, or 2 points for length of follow-up:
- Follow-up period (< 5 years, 5 to 10 years, > 10 years).

Extra points (1 for each, with a maximum of 9 points):
0 to 5 points:
- Matching on socio-economic data,
- matching of date of admission,
- histological proof of colorectal cancer (rather than radiological),
- multicentre (same country).

0 to 3 points:
- Allowances made for confounding factors such as fat content of diet, obesity, smoking, alcohol, or parity.

Penalty points (–1 each) for:
- Unsuitable and bad choice of controls such as left sided colon cancers, for right sided cases,
- multicentre (intercontinental or between different countries),
- mixtures of data concerning cholelithiasis with cholecystectomy.

Studies Considered: Forty-seven studies were procured as a result of the original Medline search plus the relevant references from citations. Twenty studies were