Cholecystectomy and Colorectal Cancer

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Background: An increased risk of large bowel cancer, especially of the right colon, following cholecystectomy has been reported in some studies but contradicted in others. The aim of this study was to settle this question by creating a cohort of cholecystectomy patients that was large enough and with a sufficient follow-up time to detect even weak associations.

Methods: A population-based cohort consisting of 62,615 patients who underwent cholecystectomy was followed up for the occurrence of colorectal cancer up to 23 years. Results: There were 633 colorectal cancers versus 637.9 expected (standardized incidence ratio [SIR] = 0.99; 95% confidence interval [CI] = 0.92–1.07). Analyses of an extensive number of subgroups including sex, age at operation, duration of follow-up, underlying diagnosis, type of operation, and different cancer sites did not show any association. However, for cancer of the right colon among women, the risk was increased (SIR = 1.24; 95% CI = 1.03–1.48) most prominent 15 years or more after operation (SIR = 1.54; 95% CI = 1.03–2.22). Conclusions: Overall, there is no excess risk of colorectal cancer following cholecystectomy, but consistent with some earlier reports, we observed an increased risk among women for right-sided colon cancer 15 years or more after operation.

The first report in 1978 that cholecystectomy may increase the risk of colorectal cancer stimulated a number of epidemiological studies. Some showed an increased risk, especially among women and for cancer of the proximal colon, whereas others failed to establish any association. Differences in methodology, limited follow-up, and low statistical power due to small numbers of patients are possible reasons for the inconsistent findings. Our aim was to settle this matter by means of a population-based study in an area with a high incidence of both cholecystectomies (300/105 inhabitants and year) and colorectal cancer that was large enough to detect even weak associations between cholecystectomy and cancer risk at different subsites in the large bowel.

Thus, a cohort of more than 60,000 patients with cholecystectomy was subjected to virtually complete follow-up for up to 23 years. This report is an expansion and extension of earlier studies of this issue in Uppsala, Sweden.

Material and Methods

The Cohort

The six-county Uppsala Health Care Region is located in central Sweden and had, during the study period, 1.2–1.3 million inhabitants. Because there is almost no private in-patient treatment in Sweden, hospital-provided medical services are population based and referable to the county in which the patient lives. From 1965 through 1983, the Swedish National Board of Health and Welfare received annual reports from all inpatient medical institutions in Sweden and recorded data on individual hospital admissions and discharges in the Inpatient Register. Beside national registration number, a unique personal identifier assigned to all Swedish citizens, each record contains data on surgical procedures and up to eight discharge diagnoses. These diagnoses were coded according to the seventh revision of the International Classification of Diseases (ICD-7) through 1968 and according to the eighth revision (ICD-8) thereafter. The extent of underreporting to the Inpatient Register was low, less than 2% overall.

All records in the Inpatient Register containing any of the following procedures were considered for inclusion in the study: cholecystectomy, cholecystectomy combined with choledochotomy, choledocholithotomy, choledochotomy plus sphincterotomy, or cholecystectomy combined with choledocholithotomy plus sphincterotomy. For this study, the operations were grouped into cholecystectomy only and cholecystectomy combined with any operation on the bile duct simultaneously or later at a second operation.

We excluded all patients who were assigned a cancer diagnosis at the time of the cholecystectomy. To assess possible association between the underlying disease and cancer risk, the patients were grouped into the following four mutually exclusive categories. (1) Acute cholecystitis with the following ICD-7 codes: 584.30, 584.31, 585.00, 585.01.
585.29 and ICD-8 codes: 574.00, 574.06, 575.00, 575.05. (2) Chronic cholecystitis with the following ICD-7 codes: 584.10, 584.11, 585.10, 585.19 and the ICD-8 codes: 574.01, 574.02, 575.01. (3) Cholelithiasis only with the following ICD-7 codes: 584.00, 584.01, 584.99 and the ICD-8 codes: 574.03, 574.09. (4) Others, where no presence of any stone or inflammation is mentioned in the discharge diagnosis.

In separate analyses, patients with suspected or confirmed common bile duct stones, i.e., those having a diagnosis at discharge mentioning choledocholithiasis or cholangitis, were grouped together and compared with all others.

The indication for cholecystectomy may have changed during the study period, because the annual number of cholecystectomies decreased markedly from 1965 to 1983 (Table 1). If indications for surgery are related to the risk of colorectal cancer, such changes may confound comparisons between time periods. Therefore, to control for this potential confounding, those who underwent surgery (1965–1969, 1970–1974, 1975–1979, and 1980–1983) were analyzed separately.

A total of 65,999 individuals had surgery at least once during the period of 1965 to 1983 and were thus potentially eligible. We excluded 2,254 (3.4%) individuals because they were entered in the register with an incomplete or inconsistent national registration number and thus not available for follow-up. Another 713 individuals (1.1%) were excluded because of errors in their national registration number. Finally, 145 individuals were excluded because of a diagnosis of colorectal cancer before the operation. Thus, a total of 62,615 patients (41,870 women, 20,745 men) constituted the cohort. The mean age at operation was 49.2 years for women and 55.4 years for men; 27.5% of the patients were under the age of 40, and 13.6% were 70 years or older at surgery. The distribution of the cohort members by sex, diagnosis at discharge, operative procedures, and year of operation is shown in Table 1.

**Follow-Up**

Record linkage, based on the national registration number, to the nationwide death and emigration registers led to information on the date of death or emigration through 1987. The Swedish Cancer Registry, founded in 1958, was used to ascertain all incident cancers diagnosed in the cohort from start of follow-up until the end of 1987. The time of observation was calculated from the registration date of operation until the diagnoses of colorectal cancer, death, emigration or the end of the observation period (December 31, 1987).

The expected number of cancers was calculated by multiplying the number of person-years for each sex by age-specific cancer incidence rates for each five-year age group and calendar year of observation. These expected rates were derived from the Uppsala health care region. For the main analyses, we used a one-year latency period between the date of operation and calculation of observed and expected numbers of cancers. The aim of this approach, applied in similar studies previously,30 was to eliminate or reduce the possible impact of selection bias. The cohort was analyzed for occurrence of cancers of the colon (ICD-7: 153) and rectum (ICD-7: 154), whereas the risks for right-sided colon cancer (cecum and ascending [ICD-7: 153.0]; appendix [ICD-7: 153.4]) and left-sided colon cancer (descending [ICD-7: 153.2]; sigmoid [ICD-7: 153.3]) were analyzed separately.

**Statistical Methods**

The standardized incidence ratio (SIR) was defined as the ratio of observed numbers of cancers to those expected. The 95% confidence interval (CI) of the SIR was then calculated on the assumption that the observed number follows a Poisson distribution.40 For further analyses in which each subgroup was evaluated independently, we used Poisson regression analyses.41 Underlying diagnosis at discharge, sex, type of operation, and duration of follow-up were entered in the model.

**Results**

**Univariate Analyses**

A total of 722 colorectal cancers were diagnosed during follow-up compared with 674.8 expected (SIR = 1.07; 95% CI, 0.99–1.15). After exclusion of the first postoperative year, 633 cancers occurred versus 637.9 expected (SIR = 0.99; 95% CI, 0.94–1.07).

The relative risk for colon cancer overall was close to unity (SIR = 1.03; 95% CI, 0.94–1.14) without any difference in risk after cholecystectomy only (SIR = 1.04; 95% CI, 0.94–1.16) or cholecystectomy combined with an operation on the bile duct (SIR = 0.99; 95% CI, 0.78–1.23). Nor were time period of opera-
tion or underlying diagnoses at discharge or a history with and without common bile stones associated with appreciable differences in relative risk.

The risk for right-sided cancer of the colon was nonsignificantly increased (SIR = 1.15; 95% CI, 0.98–1.33); cholecystectomy alone entailed a slightly higher risk (SIR = 1.17; 95% CI, 0.99–1.38) than a combined operation (SIR = 1.03; 95% CI, 0.70–1.47). None of the underlying diagnoses was associated with a significantly increased risk of right-sided cancer: acute cholecystitis (SIR = 0.98; 95% CI, 0.56–1.59), chronic cholecystitis (SIR = 1.08; 95% CI, 0.86–1.34), cholelithiasis only (SIR = 1.25; 95% CI, 0.94–1.61), and other (SIR = 1.41; 95% CI, 0.81–2.29). The risk of left-sided colon cancer was close to unity (SIR = 1.05; 95% CI, 0.89–1.23). Type of operation, underlying diagnosis, or time period did not alter the risk estimates for left-sided colon cancer.

The overall number of rectal cancers was nonsignificantly lower than expected (SIR = 0.92; 95% CI, 0.80–1.05). Patients with cholecystectomy only had a relative risk (SIR = 0.93; 95% CI, 0.80–1.07) similar to those with a combined operation (SIR = 0.90; 95% CI, 0.66–1.21). The diagnoses at discharge did not entail any variations in risk: acute cholecystitis (SIR = 0.91; 95% CI, 0.59–1.34), chronic cholecystitis (SIR = 0.96; 95% CI, 0.79–1.14), cholelithiasis only (SIR = 0.83; 95% CI, 0.64–1.07), and other (SIR = 1.09; 95% CI, 0.68–1.67).

Stratified Analyses

In men, there were 138 observed cases of colon cancer versus 148.0 expected (SIR = 0.93; 95% CI, 0.78–1.10) for 1–23 years after operation. The corresponding numbers for women were 276 observed versus 252.6 expected (SIR = 1.09; 95% CI, 0.97–1.23). Duration of follow-up did not affect the risk estimates, which were consistently somewhat lower among men than women (Table 2).

Among men, 52 cases of cancer occurred in the right colon (SIR = 0.98; 95% CI, 0.73–1.28). Among women, a slightly increased risk was found based on 121 cases (SIR = 1.24; 95% CI, 1.03–1.48). This elevated risk occurred in both younger (<50 years) and older (≥50 years) women but showed no clear trend with duration of follow-up, although the highest risk estimates occurred 15 or more years after operation (Table 3). Younger men (<50 years) also tended to have higher risks, particularly at 15 or more years since operation. Analyses stratified for underlying diagnosis and duration of follow-up revealed that chronic cholecystitis was most consistently associated with risk for right-sided colon cancer 15 or more years after operation (SIR = 1.60; 95% CI, 1.01–2.40), both for men (SIR = 1.45; 95% CI, 0.58–2.99) and women (SIR = 1.67; 95% CI, 0.96–2.72). In contrast, risk estimates close to unity were found among patients with acute cholecystitis (SIR = 1.01; 95% CI, 0.12–3.65), cholelithiasis only (SIR = 1.18; 95% CI, 0.59–2.11), and other discharge diagnoses (SIR = 0.60; 95% CI, 0.01–3.32).

The risk for left-sided colon cancer was similar among men (SIR = 0.99; 95% CI, 0.73–1.29) and women (SIR = 1.09; 95% CI, 0.88–1.33), without evidence of any trend with duration of follow-up (Table 4). Analysis of the risk for cancer in other sites of colon, i.e., transverse colon and unspecified site, did not yield any additional information.

For rectal cancer, the risks were similar among men (SIR = 0.94; 95% CI, 0.76–1.14) and women (SIR = 0.91; 95% CI, 0.76–1.09) (Table 5). The risk tended to decrease the longer the follow-up was for all patients, but this trend was not consistent when analyzing men and women separately.

Multivariate Analyses

Poisson regression models were fitted with sex, type of operation, underlying diagnosis, follow-up, and an interaction term for sex and follow-up time as independent variables. Separate models were fitted for all colon cancer and right and left-sided colon cancer. None of the variables or interaction terms differed significantly from the reference value in any of the models when tested against a χ² distribution.

| Table 2. SIR of Colon Cancer by Gender and Duration Since Cholecystectomy |
|------------------|------------------|------------------|
| Duration of follow-up (yr) | n | SIR (95% CI) | n | SIR (95% CI) | n | SIR (95% CI) |
| 1–4 | 66 | 1.10 (0.85–1.40) | 39 | 0.94 (0.67–1.29) | 105 | 1.03 (0.85–1.25) |
| 5–9 | 94 | 1.22 (0.99–1.49) | 44 | 0.92 (0.67–1.24) | 138 | 1.11 (0.93–1.31) |
| 10–14 | 65 | 0.97 (0.75–1.23) | 32 | 0.90 (0.61–1.26) | 97 | 0.94 (0.76–1.15) |
| ≥15 | 51 | 1.00 (0.79–1.39) | 23 | 1.00 (0.63–1.49) | 74 | 1.04 (0.62–1.30) |
| Totals | 276 | 1.09 (0.97–1.23) | 138 | 0.93 (0.78–1.10) | 414 | 1.03 (0.94–1.14) |
Table 3. SIR of Right-Sided Colon Cancer by Gender, Duration Since Cholecystectomy, and Age at Operation

<table>
<thead>
<tr>
<th>Duration of follow-up (yr)</th>
<th>&lt;50 yr old</th>
<th>≥50 yr old</th>
<th>All</th>
<th>&lt;50 yr old</th>
<th>≥50 yr old</th>
<th>All</th>
<th>Both sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
<td></td>
<td>Women</td>
<td>Men</td>
<td></td>
<td>Both sexes</td>
</tr>
<tr>
<td></td>
<td>SIR (95% CI)</td>
<td>SIR (95% CI)</td>
<td></td>
<td>SIR (95% CI)</td>
<td>SIR (95% CI)</td>
<td></td>
<td>SIR (95% CI)</td>
</tr>
<tr>
<td>1-4</td>
<td>4</td>
<td>2.04 (0.56-5.25)</td>
<td>26</td>
<td>1.25 (0.82-1.84)</td>
<td>30</td>
<td>1.32 (0.89-1.89)</td>
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</tr>
<tr>
<td>5-9</td>
<td>4</td>
<td>1.18 (0.32-3.03)</td>
<td>30</td>
<td>1.13 (0.76-1.61)</td>
<td>34</td>
<td>1.13 (0.78-1.58)</td>
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</tr>
<tr>
<td>10-14</td>
<td>2</td>
<td>0.50 (0.06-1.79)</td>
<td>26</td>
<td>1.17 (0.76-1.71)</td>
<td>28</td>
<td>1.06 (0.71-1.54)</td>
<td>2</td>
</tr>
<tr>
<td>≥15</td>
<td>8</td>
<td>1.86 (0.81-3.71)</td>
<td>21</td>
<td>1.44 (0.89-2.21)</td>
<td>20</td>
<td>1.64 (1.03-2.22)</td>
<td>4</td>
</tr>
<tr>
<td>Totals</td>
<td>18</td>
<td>1.32 (0.78-2.09)</td>
<td>103</td>
<td>1.22 (1.00-1.46)</td>
<td>121</td>
<td>1.24 (1.03-1.48)</td>
<td>9</td>
</tr>
</tbody>
</table>

Discussion

By showing a SIR of 0.99 (95% CI, 0.92-1.07) after excluding the first year of follow-up, this study appears to rule out an overall association between cholecystectomy and subsequent risk of colorectal cancer. Multivariate analyses further indicated that no subgroup with a significantly increased or decreased risk could be defined by sex, underlying diagnosis, features of surgery, or duration of follow-up. However, some subgroups were identified in the stratified analysis where an association may exist. In particular, women had a significantly increased risk for right-sided colon cancer, especially at 15 or more years after cholecystectomy and at a young (<50 years) age at operation. A similar trend was also apparent among young men (<50 years).

Three previous cohort studies of colorectal cancer after cholecystectomy have been published.8,26,27,35 Earlier reports,26,27 comprising about one fourth of the patients included in this study, revealed no overall increased risk for all colon or rectal cancer, albeit with a shorter follow-up, 14-17 years,27 and without separate analyses by underlying diagnosis or site of colon cancer. Linos et al.8 reported a nonsignificantly increased risk of colorectal cancer overall and a significantly (relative risk = 2.1; 95% CI, 1.1-3.6) increased risk of right-sided colon cancer among women. The duration of follow-up varied between 10 to 29 years, but there was no examination by time since operation, and only those diagnosed with a cancer within 6 months after operation were excluded. The third study35 was small (464 patients) and lacked the statistical power to detect any association.

Most case-control studies published thus far report a relative risk of 1.5-2.5 for colon cancer following cholecystectomy.5,7,16 The increased risk was mostly confined to the proximal colon,3,4,20 and/or to women.13,21,22,33 Substantially higher relative risks, up to 4.0, were found12,15,17 in studies that included cancers during the first year after operation. In those instances where duration since cholecystectomy has been analyzed,3,6,16,20,33 an average time period of slightly <20 years since operation was associated with the highest risk for colon cancer. There have also been reports of no association between cholecystectomy and colon cancer, but those studies were small28-31,36 or had risk estimates derived through comparisons involving colon sites25,32 or other malignancies.34,37

According to a leading hypothesis, the continuous secretion of bile into the gut after removing the gallbladder leads to increased enterohepatic circulation and enhanced formation of carcinogenic secondary

Table 4. SIR of the Left-Sided Colon Cancer by Gender and Duration Since Cholecystectomy

<table>
<thead>
<tr>
<th>Duration of follow-up (yr)</th>
<th>Women</th>
<th>Men</th>
<th>Both sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>SIR (95% CI)</td>
<td>n</td>
</tr>
<tr>
<td>1-4</td>
<td>20</td>
<td>0.88 (0.54-1.35)</td>
<td>16</td>
</tr>
<tr>
<td>5-9</td>
<td>40</td>
<td>1.43 (1.02-1.95)</td>
<td>14</td>
</tr>
<tr>
<td>10-14</td>
<td>24</td>
<td>1.03 (0.66-1.53)</td>
<td>17</td>
</tr>
<tr>
<td>≥15</td>
<td>14</td>
<td>0.89 (0.49-1.49)</td>
<td>8</td>
</tr>
<tr>
<td>Totals</td>
<td>98</td>
<td>1.09 (0.86-1.33)</td>
<td>55</td>
</tr>
</tbody>
</table>
The increased proliferative activity in the colon mucosa after cholecystectomy supports this hypothesis. In mice given carcinogens (e.g., dimethylhydrazine), a higher incidence of colon cancer was found after cholecystectomy than after sham operation.

Patients with acute cholecystitis or with cholelithiasis may have a functional gallbladder until obstructive symptoms require operation. Patients with chronic cholecystitis, on the other hand, probably have periods with a nonfunctional gallbladder before cholecystectomy. Thus, it is noteworthy that we found an increased risk of right-sided colon cancer 15 years after cholecystectomy limited to patients with an underlying diagnosis of chronic cholecystitis, suggesting the influence of a nonfunctional gallbladder and not gallstone disease as such for intervals that may exceed 15–20 years.

We found a slightly lower-than-expected incidence of rectal cancer that was in agreement with our earlier analyses and two other reports. In the majority of studies, no association was observed, although two reported an increased risk, making it unlikely that any association exists between cholecystectomy and rectal cancer.

Closer surveillance of patients who have undergone cholecystectomy has been proposed as a likely explanation for the reported association with right-sided colon cancer. However, if such a bias exists, the increased risk should be independent of the follow-up period and not restricted to 15 or more years after operation. Another concern is the many stratifications and comparisons made in this study, and an explanation for our finding of an increased risk of right-sided colon cancer among women could, therefore, be a type I error. However, this was a subgroup of special interest due to the large number of previous papers suggesting such an association, which makes it unlikely that such an error is operating. Thus, the excess risk for right-sided colon cancer among women 15 years or more after cholecystectomy, although of a lesser magnitude than previously reported, probably is a reality. However, the magnitude of this excess risk is low and nonexistent when analyzing colorectal cancer as one entity, and no specific follow-up of this patient group is warranted.

In summary, the absence of an overall increased risk of colorectal cancer after cholecystectomy in an area with a high incidence of both cholecystectomy and colorectal cancer independent of duration of follow-up is reassuring. However, consistent with some earlier reports, we observed an increased risk among patients, particularly women, for right-sided colon cancer 15 or more years after operation.

References

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Received September 28, 1992. Accepted January 19, 1993.

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