# Increased Risk of Colorectal Cancer among Patients with Biliary Tract Inflammation: A Five-year Follow-Up Study

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**Novelty and impact of this paper**: No population-based study has ever been conducted to explore the relationship between patients with biliary tract inflammation (BTI) and the risk of colorectal cancer. We found that the adjusted hazard ratios for colorectal cancer for patients with BTI were 6.54-times as high as for those without BTI within a 1-year follow-up period.

## Abstract

The purpose of the study was to investigate the risk of colorectal cancer among patients with biliary tract inflammation (BTI) compared to non-BTI patients during a 5-year follow-up period. The study group comprised 1613 patients with BTI, among which 32 cases (1.98%) developed colorectal cancer. The comparison group included 8065 randomly selected subjects (five for every patient with BTI), 74 of whom contracted colorectal cancer (0.92%). Stratified Cox proportional hazard regressions were calculated to estimate the adjusted hazard of colorectal cancer between the study group and comparison group. The adjusted hazard ratio for colorectal cancer for patients with BTI was 6.54-times (95% CI = 3.07-13.92) as high as for those without BTI within a 1-year follow-up period, 3.20-times (95% CI = 1.93-5.30) as high within a 3-year follow-up period, and 2.21-times (95% CI = 1.45-3.37) as high within a 5-year follow-up period. We also found that the adjusted hazard ratio for colorectal cancer for those with bile duct inflammation was 3.30-times (95% CI = 1.87-5.84) as high as for those without BTI within the five-year follow-up period. However, no increased hazard of colorectal cancer was observed for patients with gallbladder inflammation. We concluded that patients with BTI had a significantly higher risk of colorectal cancer compared to patients without BTI.


**Key words**: biliary tract inflammation; colorectal cancer; epidemiology

## Introduction

Biliary tract inflammation (BTI), including cholecystitis and cholangitis, both infectious and non-infectious types, refers to an inflammation of the gallbladder and bile duct. BTI, a common illness,[1,2] is a significant cause of morbidity and mortality worldwide, particularly in older patients with comorbid diseases.[3-8] Although endoscopic, percutaneous, and surgical treatments are commonly available for BTI in recent years, BTI still carries a mortality rate of 10%-20%.[9-11]

On the other hand, colorectal cancer is a major global health problem and is the third most common cancer in the US and Taiwan.[12-15] Since exposure to risk factors can increase the development of such neoplasms, modification of risk factors for colorectal cancer to prevent its occurrence can significantly reduce societal impacts of this neoplasm disorder.

During the past decade, plenty of studies have reported that associated inflammatory processes can increase the risk of developing ovarian, oral, and colorectal cancers.[16-20] In particular, one study by Triantafillidis et al. documented that the presence of inflammatory manifestations resulting from cholangitis might increase the risk of colorectal cancer.[21] In addition, BTI can increase serum bile acid concentrations, which might result in an elevated risk of colorectal cancer.[22] However,

according to our knowledge, no population-based study has ever been conducted to explore the relationship between BTI and the risk of colorectal cancer.

Therefore, the aim of this study was to investigate the risk for colorectal cancer among BTI patients during a 5-year follow-up period after establishment of a diagnosis of BTI, compared to non-BTI patients during the same period, while adjusting for sociodemographic characteristics.

## Materials and Methods

### Database

In this study, we used the "Longitudinal Health Insurance Database 2005 (LHID2005)" released by the Taiwan National Health Research Institute (NHRI) in 2006. Taiwan implemented its National Health Insurance (NHI) program in 1995 to provide affordable health care for all the island's residents. There are currently 25.68 million enrollees covered by the program, representing over 98% of the island's population. The LHID2005 contains all the medical claims data as well as a registry of 1,000,000 persons, randomly sampled from the 25.68 million enrollees covered by the NHI. The Taiwan NHRI reports that there were no statistically significant differences in age, sex, or healthcare costs between the sample group and all enrollees. Therefore, the LHID2005, a nationwide population-based dataset, provides an excellent opportunity to examine the risk of colorectal cancer among patients with BTI.

Since the dataset used in this study consisted of de-identified secondary data released to the public for research purposes, this study was exempt from full review by the Institutional Review Board.

### Study Sample

We selected patients who visited ambulatory care centers or were hospitalized with a principal diagnosis of BTI (ICD-9-CM codes 575.0, 575.1, 575.2, 576.1, or 576.2) between January 1, 1999 and December 31, 2001 (*n*=1,686) for the study group. We excluded patients who had had any type of cancer (ICD-9-CM codes 140-239) or BTI diagnosis during the previous 3-year period (*n*=72). We also excluded patients with comorbid inflammatory bowel disease (*n*=1). Ultimately, our study cohort included 1,613 patients with BTI.

The comparison group was selected from the remaining persons in the LHID2005. We randomly selected 8065 enrollees (five for every patient with BTI) from the registry of persons, matched with the study group in terms of age (< 45, 45-64, 65-74 and > 74 years) and sex. We assigned their first ambulatory care visit between January 1, 2001 and December 31, 2001 as the index ambulatory care visit. Ultimately, 9,678 patients were included in our study. These patients had no history of BTI or cholecystectomy during the period from 1996 to 2006. However, since the NHI program in Taiwan was initiated in 1995, the dataset used in the present study only allowed us to trace use of medical services from 1996 to 2006. Therefore, we could not exclude patients who may have had BTI or cholecystectomy before 1996. Each patient was individually tracked for 5 years from their index outpatient visit to identify all who developed colorectal cancer (ICD-9-CM codes 153.XX or 154.XX).

Since the National Health Insurance Research Database allows us to trace all medical service utilization for all enrollees, it was possible to follow all sampled patients throughout the study period.

**Statistical Analysis**

The SAS statistical package (SAS System for Windows, vers. 8.2) was used to perform all statistical analyses in this study. We used Pearson $\chi^2$ tests to examine differences in sociodemographic characteristics (age, sex, monthly income, level of urbanization, and the geographic location of the community in which the patient resided, i.e., northern, central, eastern, and southern Taiwan) between the study and comparison groups. Monthly income was grouped into four categories: < NT$15,000, NT$15,000-30,000, NT$30,001-50,000, ≥ NT$50,001 (US$1.00 = NT$33.00 in 2003). Urbanization levels in Taiwan were divided into five strata, with level 1 referring to the 'most urbanized' and level 5 referring to the 'least urbanized' communities based on criteria used in prior studies. We calculated the 5-year colorectal cancer-free survival rate and examined differences in the risk for colorectal cancer between the two groups. Furthermore, Stratified Cox proportional hazard regressions (stratified by age and sex) were calculated to estimate the hazard of colorectal cancer for the study and comparison groups, after adjusting for monthly income, level of urbanization, and

the geographic location of the sampled patients. Differences were considered significant if a two-sided $p$ value was $\leq 0.05$.

## RESULTS

Table 1 presents a comparison of sociodemographic characteristics for patients with and without BTI. The mean age of the study sample was 53.9 years, with a standard deviation of 17.8 years. The majority of patients were between 45 and 64 years, and only 9.4% of the sampled patients were over 74 years old. After matching the patient age and sex, we found no significant differences between these two groups in the level of urbanization or geographic location of the community in which the patient resided (Table 1).

<Insert Table 1 here>

Of the total sample of 9678 patients, 106 patients (1.10%) developed colorectal cancer during the 5-year follow-up period, 32 (1.98% of patients with BTI) from the study group and 74 (0.92% of patients without BTI) from the comparison group (Table 2). The results of the Kaplan-Meier survival analysis are displayed in Figure 1. The log-rank test showed that patients with BTI had significantly lower 5-year colorectal cancer-free survival rates than patients without BTI ($p$<0.001).

<Insert Table 2 and Figure 1 here>

Table 2 also presents the percentages of colorectal cancer within the 1-, 3-, and 5-year follow-up periods after the index ambulatory care visit for patients in these two groups. Compared to patients without BTI, patients with BTI had significantly higher rates of colorectal cancer within the 1-year (0.99% vs. 0.15%), 3-year (1.55% vs. 0.50%), and 5-year (1.98% vs. 0.92%) periods after their index ambulatory care visit.

The crude and adjusted hazard ratios of colorectal cancer within the 1-, 3-, and 5-year follow-up periods after the index ambulatory care visits are presented in Table 2. After adjusting for patient's level of urbanization, and the geographical location of the community in which the patient resided, compared to those patients without BTI, the hazard ratio for colorectal cancer for those with BTI were 6.54-times (95% CI = 3.07-13.92) as high within the 1-year follow-up period, 3.20-times (95% CI = 1.93-5.30) as high within the 3-year follow-up period, and 2.21-times (95% CI = 1.45-3.37) as high within the 5-year follow-up period.

We further analyzed the risk of colorectal cancer between BTI patients who did and did not undergo cholecystectomy during the follow-up period. We found that six of the BTI patients who underwent cholecystectomy (1.7% of BTI patients who underwent cholecystectomy) and 26 patients who did not undergo cholecystectomy (2.1% of BTI patients who did not undergo cholecystectomy) developed colorectal

cancer during the five-year follow-up period. No significant difference in the risk of colorectal cancer between BTI patients who did and did not undergo cholecystectomy was observed.

In addition, we examined crude and adjusted hazard ratios of colorectal cancer within the five-year follow-up period after the index ambulatory care visit, stratified by the type of BTI (gallbladder inflammation vs. bile duct inflammation) and gender. Table 3 shows that the adjusted hazard ratio for colorectal cancer for those with bile duct inflammation was 3.30-times (95% CI = 1.87-5.84) as high as those without BTI over the five-year follow-up period. However, no increased hazard of colorectal cancer was observed for patients with gallbladder inflammation. Among female patients, the adjusted hazard of colorectal cancer during the five-year follow-up period was 2.53 (95% CI = 1.44-4.41) times greater for those with BTI than for those in the comparison group.

<Insert Table 3 here>

## Discussion

As far as we know, this is the first population-based follow-up study to examine the risk for subsequent colorectal cancer among patients with BTI. Our results indicate that patients with BTI had significantly higher risk of colorectal cancer compared to patients without BTI; the risks of colorectal cancer for patients with BTI were 6.54-, 3.20-, and 2.21-times as high in the 1-, 3-, and 5-year follow-up periods, respectively, as for patients without BTI, after adjusting for sociodemographic characteristics. Our findings agree with a related study by Broome and Bergquist[23] which concluded that cholangitis appearing on the ground of ulcerative colitis increased the risk of colorectal cancer by 4.8-times in patients with ulcerative colitis without cholangitis. In addition, our study found that there was no significant difference in the risk of colorectal cancer between BTI patients who did and did not undergo cholecystectomy. This finding is also consistent with prior studies by Friedman et al. and Adami et al. which concluded that cholecystectomy did not increase the subsequent risk of colorectal cancer.[24,25]

The mechanism underlying the association between BTI and colorectal cancer is still unclear. It is possible that the excessive production of bile acid during the inflammatory process in the gallbladder and bile duct might play an important role in colorectal carcinogenesis. An inflammatory process in the biliary tract may cause more bile acid to be excreted into the intestines and, in turn, absorbed into the blood. Both a

higher unconjugated deoxycholic acid concentration in serum and a higher bile acid level in feces were correlated with higher incidences of colorectal cancer.[26] Bile acids in the colon directly stimulate the colorectal mucosal epithelium and facilitate the carcinogenesis process.[27,28] It also explains why the risk of colorectal cancer decreases with time since the BTI event, because the stimulating effect reaches a peak when BTI occurs and then is ameliorated in later years.

Furthermore, it was reported that approximately one-fifth of cancers worldwide are caused by infection.[29] Inflammation resulting from infection is considered to be an important factor contributing to tumorigenesis and tumor progression.[30] In addition, many studies implicated inflammation as a cause of pancreatic, bladder, and colorectal cancers.[31-33]

Because BTI brings patients to the attention of medical personnel, we also examined the occurrence of renal tumors, another kind of abdominal tumor, in these two groups to test this effect. We found there was no significant difference in renal tumor incidences between these two groups (8 cases in the BTI group and 21 cases in the comparison group, $p$=0.114). Accordingly, the possibility that receiving medical attention for BTI contributes to the elevated odds of contracting colorectal cancer is discounted.

The strength of our study lies in its longitudinal database and large population size. Nevertheless, the findings of this study need to be interpreted with awareness of several limitations. First, prior studies demonstrated that a family history of colorectal cancer increases the risk of colorectal cancer.[21] However, the dataset used in this study does not provide information which can be used to establish family histories of colorectal cancer. Second, the dataset used in the study lacks information on body mass index, obesity, smoking habits, alcohol use, the amount of daily fiber intake and household monthly income. These factors were demonstrated to be associated with an increased risk of colorectal cancer.[34,35]

This study found that patients with BTI had a significantly higher risk of contracting colorectal cancer compared to patients without BTI, and the risk seemed to come from bile acid stimulation, which is more highly produced during biliary tract inflammation. Therefore, further studies are also recommended to test the ameliorating effect of a bile shunting maneuver in BTI treatment.

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*Table 1 Patients with biliary tract inflammations and a comparison group in relation to sociodemographic characteristics in Taiwan, 1999-2001 (*n=*9678)*

| Variable | Patients with biliary tract inflammation | | Comparison cohort | | *p* value |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| Sex | | | | | 1.000 |
| Male | 924 | 57.28 | 4620 | 57.28 | |
| Female | 689 | 42.72 | 3445 | 42.72 | |
| Age (years) | | | | | 1.000 |
| < 45 | 469 | 29.08 | 2345 | 29.08 | |
| 45-64 | 663 | 41.10 | 3315 | 41.10 | |
| 65-74 | 329 | 20.40 | 1645 | 20.40 | |
| > 74 | 152 | 9.42 | 760 | 9.42 | |
| Urbanization level | | | | | 0.300 |
| 1 | 295 | 18.28 | 1479 | 18.34 | |
| 2 | 251 | 15.56 | 1395 | 17.30 | |
| 3 | 144 | 8.93 | 764 | 9.47 | |
| 4 | 134 | 8.31 | 692 | 8.58 | |
| 5 | 789 | 48.92 | 3735 | 46.31 | |
| Geographic region | | | | | 0.271 |
| Northern | 1095 | 67.89 | 5511 | 68.33 | |
| Central | 199 | 12.34 | 1095 | 13.58 | |
| Southern | 296 | 18.35 | 1342 | 16.64 | |
| Eastern | 23 | 1.43 | 117 | 1.45 | |

*Table 2 Hazard ratios (HRs) of colorectal cancer development among sample patients during the 1-, 3-, and 5-year follow-up periods after discharge from the index ambulatory care visit, 1999-2001* [a]

| Development of colorectal cancer | Total | | Patients with biliary tract inflammation | | Comparison cohort | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Panel A: One-year follow-up period | | | | | | |
| Yes | 28 | 0.29 | 16 | 0.99 | 13 | 0.15 |
| No | 9650 | 99.71 | 1597 | 99.01 | 8052 | 99.85 |
| Crude HR (95% CI) | – | | 1.00 | | 6.72*** (3.18-14.24) | |
| Adjusted HR (95% CI) | – | | 1.00 | | 6.54*** (3.07-13.92) | |
| Panel B: Three-year follow-up period | | | | | | |
| Yes | 65 | 0.67 | 25 | 1.55 | 40 | 0.50 |
| No | 9613 | 99.33 | 1588 | 98.45 | 8025 | 99.50 |
| Crude HR (95% CI) | – | | 1.00 | | 3.16*** (1.91-5.22) | |
| Adjusted HR (95% CI) | – | | 1.00 | | 3.20*** (1.93-5.30) | |
| Panel C: Five-year follow-up period | | | | | | |
| Yes | 106 | 1.10 | 32 | 1.98 | 74 | 0.92 |
| No | 9572 | 98.90 | 1581 | 98.02 | 7991 | 99.08 |
| Crude HR (95% CI) | – | | 1.00 | | 2.19*** (1.44-3.32) | |
| Adjusted HR (95% CI) | – | | 1.00 | | 2.21*** (1.45-3.37) | |

* Total sample number = 9.678.

† Adjustments (stratified by age and sex) were made for patient's geographical region and urbanization level.

‡ *** indicates $p<0.001$.

CI, confidence interval.

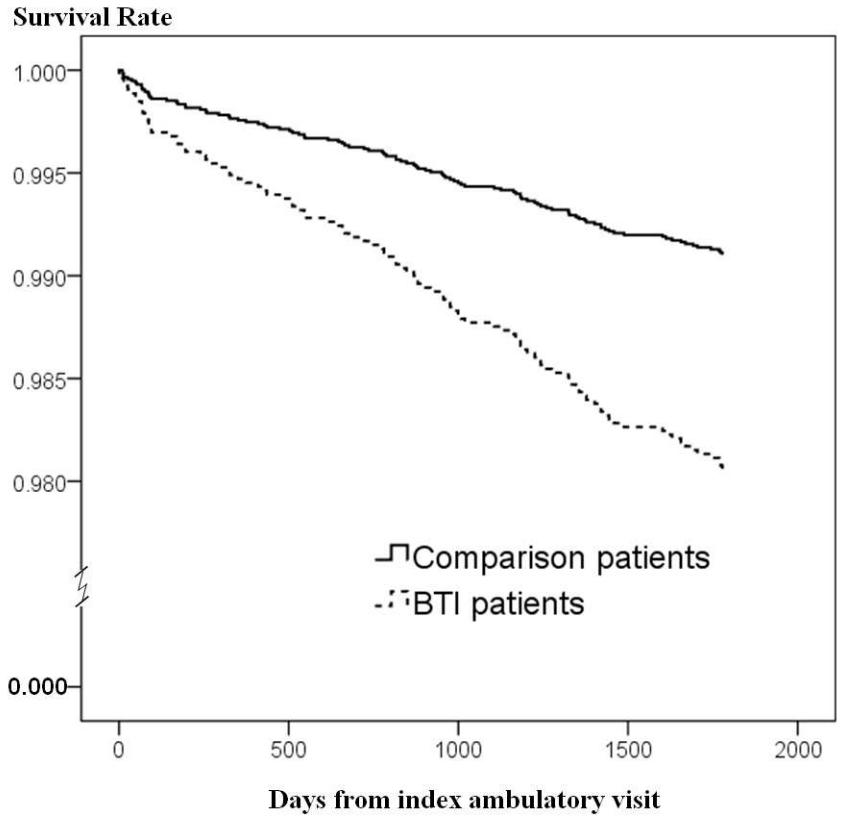
*Table 3 Hazard ratios (HRs) of colorectal cancer development among sample patients during the 5-year follow-up periods after discharge from the index ambulatory care visit, 1999-2001 by type of biliary tract inflammation and by gender*

| Development of colorectal cancer | Total | | | Male | | Female | |
|---|---|---|---|---|---|---|---|
| | Comparison Cohort (*n*=8,065) | Patients with biliary tract inflammation | | | | | |
| | | Patients with gallbladder Inflammation (*n*=1,131) | Patients with bile duct Inflammation (*n*=482) | Comparison Cohort (*n*=3,445) | Patients with biliary tract inflammation (*n*=689) | Comparison Cohort (*n*=4,620) | Patients with biliary tract inflammation (*n*=924) |
| Yes, *n*,% | 74 (0.9) | 17 (1.5) | 15 (3.1) | 36 (1.0) | 13 (1.9) | 38 (0.8) | 19 (2.1) |
| No, *n*,% | 7,991 (99.1) | 1,114 (98.5) | 467 (96.9) | 3,409 (99.0) | 676 (98.1) | 4,582 (99.2) | 905 (97.9) |
| Crude HR (95% CI) | 1.00 | 1.65 (0.97-2.80) | 3.47***(1.98-2.80) | 1.00 | 1.82 (0.96-3.45) | | 2.53***(1.45-4.41) |
| Adjusted HR (95% CI) | 1.00 | 1.71 (0.99-2.92) | 3.30***(1.87-5.84) | 1.00 | 1.84 (0.95-3.54) | | 2.53**(1.44-4.41) |

‡ ** indicates $p<0.01$*** indicates $p<0.001$.

**Caption**

*Figure 1. Colorectal cancer-free survival rates of patients with biliary tract inflammation and a comparison group in Taiwan, 1999-2001.*

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