The Risk of Colorectal Neoplasia in Patients with Gallbladder Diseases

Sung Noh Hong, Tae Yoon Lee, and Sung-Cheol Yun

INTRODUCTION

Colorectal cancer is potentially preventable if premalignant adenomas are detected and removed during colonoscopy before they become malignant (1, 2). Consequently, the etiologies and risk factors of colorectal adenomas have become the focus of attention with regard to strategies for the prevention and screening of colorectal cancer.

The relationship between cholecystectomy and colorectal cancer has been investigated extensively and their association has been demonstrated (3-7). By contrast, little is known about the relationship between colorectal neoplasia (CRN) including adenoma and cancer and gallbladder diseases, such as gallstone and gallbladder polyps, in patients with an intact gallbladder (8-12). Several studies investigating the association of gallbladder disease with CRN have suggested a relationship between gallbladder polyps and colorectal adenoma (9), whereas evidence of a relationship between gallstones and CRN is conflicting (8, 10-12).

The co-occurrence of CRN and gallbladder disease is suggested by the similar risk factors for gallstones, gallbladder polyps, and CRN, including older age, obesity, metabolic syndrome, glucose intolerance, and hyperlipidemia (13-17), and by the similarities between the epithelium of the gallbladder and that of the colonic mucosa (18). Thus, the aim of our hospital-based case-control study was to investigate the prevalence of CRN in patients with gallbladder diseases, including gallstone and gallbladder polyps, and to identify the predisposing factors for their association.

MATERIALS AND METHODS

Study population

This cross-sectional study was based on a consecutive series of participants in a colonoscopy and ultrasonography-screening program between January 2011 and December 2011 as part of a health check-up at the Healthcare Center of Konkuk University Medical Center in Seoul, Korea. The details of the examination were described previously (15). Various examination procedures, including ultrasonography and colonoscopy, are available at our center. Most of the study participants were examined as part of an employee health check-up paid for by their companies. Others paid for their health screening examinations themselves. Individuals screened in the health check-up program received written information about the screening program, including a toll-free telephone number to call to obtain more in-
formation about the program and/or to schedule an appointment for screening. Telephone interviews were conducted by experienced nurses to establish that the examinees who called to make an appointment for screening were asymptomatic. Individuals with symptoms were urged to seek medical care from their usual healthcare providers. One week before the check-up, screening participants received a standard questionnaire that included questions regarding their personal medical history (including history of CRNs), present medications, family history (including colorectal cancer in first-degree relatives), and lifestyle habits (including smoking and alcohol consumption).

On the day of the health check-up, physical examinations, anthropometry, laboratory assays (including serum glucose and triglyceride levels), imaging studies (including abdominal ultrasonography), and endoscopies (including colonoscopy) were performed after the patients had fasted for at least 12 hr. Ultrasound technicians and colonoscopists were not given the results of each other’s examinations. The examination data were recorded electronically in a centralized digital medical record system. At our center, a prospective registry of health check-up participants was constructed in January 2010 by data retrieval from the centralized digital medical record system.

The exclusion criteria were as follows: (i) incomplete questionnaire or refusal to answer the questionnaire, (ii) possible symptoms associated with gallbladder disease or CRN (abdominal pain, recent changes in bowel habits, or visible rectal bleeding), (iii) a history of colorectal polyp or cancers, (iv) a history of colorectal resection, (v) a history of cholecystectomy, (vi) inflammatory bowel disease.

Colonoscopy
All colonoscopies conducted for screening purposes were high-definition colonoscopies (CF-H260AI, Olympus, Tokyo, Japan; or an EC-3490Fi, Pentax, Tokyo, Japan) performed by eight experienced endoscopists. Withdrawal times were adjusted to a minimum of 6 min per colonoscopy to allow for adequate inspection. During colonoscopy, the location, number, and size of any CRNs were recorded. Histologically confirmed adenocarcinomas or adenomas were considered as CRNs. An advanced CRN was defined as an invasive cancer or adenoma that was ≥ 10 mm in diameter and had high-grade dysplasia or a significant villous component.

Ultrasonography
After overnight fasting and prior to colonoscopy, participants underwent abdominal ultrasonography using an iU22 ultrasound system (Philips Healthcare, Bothell, WA) with a 3.5-MHz convex probe and performed by five experienced radiologists. Gallstones were diagnosed as mobile echoes, usually throwing a shadow, in the gallbladder lumen (19). Gallbladder polyps were diagnosed as immobile echoes protruding from inside the gallbladder wall into the lumen (19). Gallbladder adenomyomatosis was diagnosed as diffuse or segmental thickening of the gallbladder wall and by the appearance of anechoic intramural diverticula on ultrasonography (19). Ultrasonography was conducted as a screening test, not corresponding to any symptoms or abnormal blood chemistry.

Definitions
Glucose intolerance was defined as a fasting glucose level of ≥ 100 mg/dL. Diabetes mellitus was defined as a fasting glucose level of ≥ 126 mg/dL. Abdominal obesity was defined as a waist circumference ≥ 90 cm in males and ≥ 85 cm in females (20). Hypertriglyceridemia was defined as a fasting triglyceride level of ≥ 150 mg/dL.

Statistical analysis
Continuous variables are expressed as means ± standard deviations, and categorical variables as absolute values and percentages. Differences between continuous variables were analyzed using an unpaired Student’s t-test, and those between categorical variables using chi-square tests and Fisher’s exact tests, as appropriate. Logistic regression analysis was used to obtain the odds ratios (OR) and 95% confidence intervals (CIs) of CRN in screening participants with gallbladder diseases. To examine the potential confounders for CRN, multivariate models were adjusted for age, sex, smoking, alcohol consumption, family history of CRC, abdominal obesity, glucose intolerance or type II diabetes, and hypertriglyceridemia. A P value less than 0.05 was considered to indicate statistical significance. The analyses were performed with SPSS version 18.0 for Windows (SPSS, Chicago, IL, USA).

Ethics statement
This study was approved by the institutional review board of Konkuk University Medical Center (Protocol No. 1010339). Informed consent was waived by the board.

RESULTS
Characteristics of the study population
A consecutive series of 5,772 asymptomatic individuals who underwent screening colonoscopy and ultrasonography were assessed for eligibility. After the exclusion of 1,146 patients for one or more of the following: incomplete questionnaires (n = 175), abdominal symptoms (n = 402), colorectal resection (n = 24), cholecystectomy (n = 58), inflammatory bowel disease (n = 18), and previous history of CRN (n = 469), 4,626 patients (mean age 47.1 ± 10.7 yr; male 2,283, female 2,343) participated in the study.

Table 1 shows the baseline characteristics of the study participants. A normal gallbladder was determined in 4,103 (88.7%)
The prevalence of CRNs was significantly higher in patients with than in those without gallbladder polyps (32.2% vs. 26.8%; \( P = 0.032 \)) and in patients with than in those without gallstones (35.8% vs. 26.9%; \( P = 0.020 \)).

A subgroup analysis according to age showed that among patients aged ≥ 50 yr, the prevalence of CRN was significantly higher in those with gallbladder disease than in those with a normal gallbladder (45.7% vs. 37.8%; \( P = 0.022 \)), whereas among patients age < 50 yr there was no significant association between the two conditions (24.0% vs. 19.5%; \( P = 0.068 \)) (Table 2). In patients aged ≥ 50 yr, CRNs were significantly more prevalent in patients with than in those without gallbladder polyps (47.0% vs. 38.1%; \( P = 0.044 \)), but this was not the case for patients aged < 50 yr (24.1% vs. 19.6%; \( P = 0.104 \)). Also, according to the subgroup analysis, CRNs were not associated with gallstones in either age group.

**Table 2. The prevalence colorectal neoplasia according to gallbladder diseases by age group**

| Diseases          | No. of subjects | CRN (%) | \( P \) value | \( P \) value | OR (95% CI) | \( P \) value | OR (95% CI) | \( P \) value |
|-------------------|----------------|---------|--------------|--------------|-------------|--------------|-------------|--------------|
|                   | CRN (+) group |         | CRN (-) group |               | CRN (+) group |         | CRN (-) group |               |
| Normal gallbladder| 1,258         | 54 (4.3)| 6 (0.5)      | 0.032        | 223         | 0.002       | 1.29 (0.98-1.72) | 0.068        |
| Gallbladder disease| 2,854       | 369 (27.2)| 14 (3.3)     | 0.002       | 132         | 0.004       | 1.18 (0.84-1.67) | 0.341        |
| Gallbladder polyp | 369 (27.2)   | 119 (9.4)| 54 (4.3)     | 0.032       | 92          | 0.366       | 1.18 (0.84-1.67) | 0.341        |
| Gallstones        | 151 (33.2)   | 151 (33.2)| 54 (4.3)     | 0.032       | 7           | 0.032       | 1.18 (0.84-1.67) | 0.341        |
| Adenomyomatosis   | 17 (4.3)     | 17 (4.3) | 54 (4.3)     | 0.032       | 1           | 0.032       | 1.18 (0.84-1.67) | 0.341        |

CRN, colorectal neoplasia; OR, odds ratio; CI, confidence interval.

**Multivariate analysis of factors related to CRN**

A multivariate analysis controlling for age, sex, smoking, alcohol consumption, family history of colorectal cancer, abdominal obesity, metabolic syndrome, glucose intolerance or type II diabetes, and hypertriglyceridemia showed that gallbladder polyp was an independent risk factor for CRN (adjusted OR, 1.29; 95% CI, 1.03-1.62) whereas there was no significant association...
between gallstones and CRN (adjusted OR, 1.14; 95% CI, 0.79-1.63). Table 3 shows the results of the univariate and multivariate analyses of risk factors for CRN.

**Size and number of gallbladder polyps in relation to the risk of CRN**

In the CRN (+) group, gallbladder polyps < 5 mm had a prevalence of 6.4% (80/1,258) and those ≥ 5 mm a prevalence of 3.1% (39/1,258). In the multivariate analyses, the adjusted OR for the risk of CRN was 1.12 (95% CI, 0.85-1.46) and 1.79 (95% CI, 1.15-2.77), respectively. The prevalence of CRN increased with the increasing size of the gallbladder polyp (P = 0.022) (Table 4). The prevalence of CRN in patients with a single gallbladder polyp was 5.8% (74/1,258) while in those with multiple (≥ 2) polyps it was 3.6% (45/1,258). In the multivariate analyses, the adjusted OR for the risk of CRN was 1.34 for multiple gallbladder polyps (95% CI, 0.93-1.93), which was not statistically significant. The prevalence of CRN in patients with multiple gallbladder polyps

Table 3. Multivariate analysis of risk factors for colorectal neoplasia

| Variables                              | CRN (-) group (n = 3,386) | CRN (+) group (n = 1,258) | Multivariate analysis | OR (95% CI) | P value |
|----------------------------------------|---------------------------|---------------------------|-----------------------|-------------|---------|
| **Age (yr)**                           |                           |                           |                       |             |         |
| < 50                                   | 2,283                     | 571                       | 1                     | 2.53 (2.22-2.89) | < 0.001 |
| ≥ 50                                   | 1,085                     | 687                       |                       |             |         |
| **Sex**                                |                           |                           |                       |             |         |
| Female                                 | 1,366                     | 306                       | 1                     | 1.97 (1.67-2.33) | < 0.001 |
| Male                                   | 2,002                     | 952                       |                       |             |         |
| **Smoking**                            |                           |                           |                       |             |         |
| < 20 pack-year                         | 2,988                     | 987                       | 1                     | 1.41 (1.17-1.71) | < 0.001 |
| ≥ 20 pack-year                         | 380                       | 271                       |                       |             |         |
| **Alcohol consumption**                |                           |                           |                       |             |         |
| < 30 g/day                             | 2,884                     | 1,008                     | 1                     | 1.14 (0.95-1.38) | 0.156   |
| ≥ 30 g/day                             | 484                       | 250                       |                       |             |         |
| **Family history of colorectal cancer**|                           |                           |                       |             |         |
| -                                      | 3,246                     | 1,209                     | 1                     | 1.08 (0.77-1.51) | 0.626   |
| +                                      | 122                       | 49                        |                       |             |         |
| **Metabolic syndrome**                 |                           |                           |                       |             |         |
| -                                      | 2,827                     | 963                       | 1                     | 1.45 (1.13-1.70) | 0.018   |
| +                                      | 541                       | 295                       |                       |             |         |
| **Abdominal obesity**                  |                           |                           |                       |             |         |
| -                                      | 2,269                     | 708                       | 1                     | 1.26 (1.09-1.45) | 0.002   |
| +                                      | 1,099                     | 550                       |                       |             |         |
| **Glucose intolerance or type II diabetes** |                           |                           |                       |             |         |
| -                                      | 2,820                     | 932                       | 1                     | 1.20 (1.01-1.42) | 0.034   |
| +                                      | 548                       | 326                       |                       |             |         |
| **Hypertension**                       |                           |                           |                       |             |         |
| -                                      | 2,658                     | 892                       | 1                     | 1.17 (0.99-1.37) | 0.066   |
| +                                      | 710                       | 366                       |                       |             |         |
| **Gallbladder polyp**                  |                           |                           |                       |             |         |
| -                                      | 3,118                     | 1,139                     | 1                     | 1.29 (1.03-1.62) | 0.029   |
| +                                      | 250                       | 119                       |                       |             |         |
| **Gallstone**                          |                           |                           |                       |             |         |
| -                                      | 3,271                     | 1,204                     | 1                     | 1.14 (0.79-1.63) | 0.482   |
| +                                      | 97                        | 54                        |                       |             |         |

CRN, colorectal neoplasia; OR, odds ratio; CI, confidence interval.

Table 4. Size and number of gallbladder polyps in relation to the risk of colorectal neoplasia

| Variables                  | CRN (-) group (n = 3,368) | CRN (+) group (n = 1,258) | Univariate analysis | Multivariate analysis | OR (95% CI) | P value |
|----------------------------|----------------------------|---------------------------|---------------------|-----------------------|-------------|---------|
| **Gallbladder polyp**      |                           |                           |                     |                       |             |         |
| Size                       |                           |                           |                     |                       |             |         |
| No polyp                   | 3,118                     | 1,139                     | 1                   | 0.008                 | 1           | 0.022   |
| Small ( < 5 mm)            | 196                       | 80                        | 1.17 (0.89-1.55)    | 0.267                 | 1.12 (0.85-1.46) | 0.422   |
| Large ( ≥ 5 mm)            | 54                        | 39                        | 1.93 (1.26-2.93)    | 0.002                 | 1.79 (1.15-2.77) | 0.010   |
| Number                     |                           |                           |                     |                       |             |         |
| No polyp                   | 3,118                     | 1,139                     | 1                   | 0.089                 | 1           | 0.065   |
| Single                     | 160                       | 74                        | 1.27 (0.95-1.68)    | 0.104                 | 1.24 (0.92-1.67) | 0.157   |
| Multiple ( ≥ 2)            | 90                        | 45                        | 1.46 (0.99-2.14)    | 0.054                 | 1.34 (0.93-1.93) | 0.121   |

CRN, colorectal neoplasia; OR, odds ratio; CI, confidence interval.
showed only a statistical trend ($P = 0.065$).

**DISCUSSION**

The association between gallbladder disease and CRN has yet to be fully investigated. In our large hospital-based cross-sectional study, we found a significant association between CRN and gallbladder polyps, especially in patients with polyps $\geq 5$ mm. These results are in agreement with a previous report of an association between gallbladder polyps and CRNs (9). In a previous, prospective study from Korea, a trend toward a higher prevalence of colorectal adenomas was shown in patients with than in those without gallbladder polyps (52.7% vs. 39.2%), but after adjusting for confounding factors the differences was not statistically significant (OR, 1.796; 95% CI, 0.986-3.269).

Gallbladder polyps and CRNs share several risk factors that might account for their association. The majority of gallbladder polyps detected by ultrasonography are cholesterol polyps, comprising 60%-70% of all gallbladder polyps (21). Cholesterol polyps are typically small (2-10 mm in diameter), pedunculated, and without neoplastic potential (22). Although the histological types of the gallbladder polyps were not confirmed by pathology in this study, the majority of gallbladder polyps were probably cholesterol polyps, because these are most common and because almost all of the gallbladder polyps (99.2%; 366/369) in this study were less than 10 mm in size. The mechanism underlying cholesterosis is believed to be associated with the absorption of cholesterol from bile or blood, changes in hepatic cholesterol metabolism, and the mucosal esterification of free sterols from bile (16). Recent experimental studies suggest that obesity can induce changes in cholesterol and bile acid metabolism by modifying the expression of genes involved in fatty acid transport and by affecting mucosal function and gallbladder motility (23-25). Several epidemiology studies also support this hypothesis. An impact of metabolic syndrome, including obesity, insulin resistance, and lipid profile abnormalities on the development of gallbladder polyps has been documented in several studies. Two case-control studies from Korea suggested that metabolic syndrome contributes to the development of gallbladder polyps (14, 26). In another large Korean study, in which 14,250 individuals were evaluated, a possible influence of obesity and hyperlipidemia on the risk of developing gallbladder polyps was determined (27). A previous study from Japan also reported that patients with gallbladder polyps were more obese than patients in the control group (28). A potential relationship between insulin resistance and the prevalence of gallbladder polyps was reported in two studies, both of which showed a 1.51- to 1.64-fold increased risk (14, 29).

The literature suggests that the risk factors for gallbladder polyps, such as obesity, metabolic syndrome, and insulin resistance, are also risk factors for CRN (17, 30-32). Several studies documented that obesity is a consistent risk factor for CRN. Among the proposed complex mechanisms, a direct relation between higher glucose and the subsequent risk of CRN and impaired insulin pathways has been suggested (17). C-peptide, a marker of insulin production, was shown to be positively related to CRN risk (33) and in an animal model, the group injected with insulin had a significantly higher incidence of CRN (34). Therefore, exposure to common risk factors and the consequence of similar metabolic pathways may influence the association between gallbladder polyps and CRNs.

We also found that the frequency of gallbladder polyps in patients aged $\geq 50$ yr was lower than that in patients aged $< 50$ yr (7.4% vs. 8.3%). This finding was not unexpected because a large Korean study showed a peak in the prevalence of gallbladder polyps in males 30-39 yr of age and in females 40-49 yr age (27). In addition, CRNs were significantly more prevalent in patients with than in those without gallbladder polyps in the age $\geq 50$ yr group (47.0% vs. 38.1%) but not in the age $< 50$ yr group. Given that there is an association between gallbladder polyps and CRNs only in individuals $\geq 50$ yr of age, it would be unlikely to change the current screening guidelines for CRN.

We did not observe an association between gallstones and CRNs after adjusting confounding variables. Studies exploring the relationship between gallstone and CRN have reported conflicting results. In studies conducted in the US and Norway, gallstones were not found to be related to CRN (10, 35), whereas in other studies from the US and in those from Japan, cholelithiasis was shown to be positively related to CRN (8, 12). As examples, in the Japanese study, the prevalence of colorectal adenoma was 29.6% (61/206) in patients with cholelithiasis compared with 17.7% (741/4187) in the controls, indicating that cholelithiasis is an independent risk factor for colorectal adenoma (OR 1.57; 95% CI, 1.14-2.18) (8). In a case-control study from the US, gallbladder diseases or stones were more prevalent in patients with colon polyps than in controls (13.1% vs. 5.2%; OR 2.72; 95% CI 2.53-2.73) (12). However, that study enrolled not only patients with gallstones but also patients with other gallbladder diseases that were not clearly defined. On the other hand, in a US study (10), gallstones were not associated with colorectal cancer (OR, 0.95; 95% CI, 0.91-0.99), and in a population-based case control study in Norway, colon cancer was less prevalent in patients with asymptomatic gallstones than in the normal control group (1.9% vs. 2.7%) (35). The reason why gallstones showed no relationship to CRN in our study is not clear. One possible mechanism, suggested by a US study, is that there is a trend towards a decreasing risk of CRN with increasing distance from the bile excretion site in association with gallstones; the odds ratios declined from 1.00 (95% CI, 0.95-1.06) in the proximal colon to 0.94 (95% CI, 0.89-1.00) in the distal colon and 0.83 (95% CI, 0.78-0.89) in the rectum (10). Thus, further investigation is required to determine the mechanism linking gallstones and CRN.
Our study had several limitations. First, there may have been selection bias because it was a hospital-based case-control study in a single institution and not a population-based study. However, the prevalence of gallbladder polyps and gallstone in our series of patients is similar to that described in previous reports of ultrasonography screening from East Asia, in which the prevalence of gallbladder polyps and gallstone was 2.2%-8.5% (29, 36-38) and 2.3%-5.3% (38-40), respectively. Second, our study may be limited by a small sample size. This study was a retrospective study, and we did not enroll a sufficient number of patients to achieve proper statistical power. A sample size of 966 cases and 966 controls will be required to achieve power of 80% with a confidence level of 5% to confirm these results. Another limitation of this study is that the histologic type of gallbladder disease was not confirmed by pathology. Last, other possible confounding factors, such as a medication history including NSAIDs, aspirin, or statins, could not be investigated because of a lack of data. Nevertheless, our results are meaningful given the large number (523) of patients with gallbladder disease, as well as the reliable definition of case and control from a single institution. To our knowledge, this is the first study to suggest an increased prevalence of CRN with the increasing size of gallbladder polyps.

In conclusion, a significant relationship is suggested between CRN and gallbladder polyps, especially those ≥ 5 mm, but not between gallstones and CRN. Large population-based case-control studies are needed to confirm the relationship between gallbladder polyps or stones and CRN.

AUTHOR CONTRIBUTION

Study design: Hong SN. Data generation and collection: Hong SN, Lee TY. Data analysis: Yoon SC. Writing and revision: Hong SN and Lee TY. Supervision of study and manuscript writing: Lee TY. Manuscript approval: Lee TY.

DISCLOSURE

The authors have no competing conflicts of interest to disclose.

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