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The Risk of Colorectal Neoplasia in Patients with Gallbladder Diseases

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Cholecystectomy is associated with an increased risk of colorectal cancer, but little is known about the relationship between gallbladder disease and colorectal adenoma. Gallbladder polyps and colorectal neoplasia (CRN) share several risk factors such as obesity, diabetes and metabolic syndrome, which might account for their association. In this study, we investigated whether asymptomatic patients with gallbladder disease are at increased risk of CRN and identified the factors to their association. The study population consisted of 4,626 consecutive, asymptomatic individuals drawn from a prospective health check-up cohort who underwent both ultrasonography and colonoscopy screening. The prevalence of CRNs in patients with gallbladder polyps or gallstones was significantly higher than that in the control group (32.1% vs. 26.8%; $P = 0.032$, 35.8% vs. 26.9%; $P = 0.020$). A multivariate regression analysis showed that gallbladder polyps were an independent risk factor for CRN [adjusted odds ratio (OR): 1.29; 95% confidence interval (CI); 1.03-1.62] whereas gallstones were not (adjusted OR: 1.14; 95% CI: 0.79-1.63). The adjusted OR for the risk of CRN was 1.12 for gallbladder polyps < 5 mm (95% CI, 0.85-1.46) and 1.79 for gallbladder polyps ≥ 5 mm (95% CI, 1.15-2.77). The prevalence of CRN increased with increasing polyp size (P trend = 0.022). Our results suggest that colorectal neoplasia is significantly related to gallbladder polyps, especially those ≥ 5 mm.

Keywords: Gallbladder; Colorectal Neoplasms; Risk Factors; Korea

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-

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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 resections, (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 md/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%)

Table 1. Baseline characteristics of study participants according to the presence of colorectal neoplasm

Variables	Total (n = 4,626)	CRN (+) group (n = 1,258)	CRN (-) group (n = 3,368)	*P* value
Age (yr), mean ± SD	47.1 ± 10.7	51.6 ± 10.4	45.5 ± 10.3	< 0.001
Age ≥ 50 yr, n (%)	1,772 (38.3)	687 (54.6)	1,085 (32.2)	< 0.001
Male, n (%)	2,954 (63.9)	952 (75.7)	2,002 (59.4)	< 0.001
Smoking (pack-year) ≥ 20 pack-year, n (%)	651 (14.1)	271 (21.5)	380 (11.3)	< 0.001
Alcohol consumption ≥ 30 g/day, n (%)	734 (15.9)	250 (19.9)	484 (14.4)	< 0.001
Family history of colorectal cancer, n (%)	171 (3.7)	49 (3.9)	122 (3.6)	0.662
Metabolic syndrome, n (%)	836 (18.1)	295 (23.4)	541 (16.1)	< 0.001
Waist circumference (cm) ≥ 90 in men or ≥ 85 in women, n (%)	1,649 (35.6)	550 (43.7)	1,099 (32.6)	< 0.001
Fasting glucose (mg/dL) ≥ 100 mg/dL or type II diabetes, n (%)	874 (18.9)	326 (25.9)	548 (16.3)	< 0.001
Triglyceride (mg/dL) ≥ 150 mg/dL, n (%)	1,076 (23.3)	366 (29.1)	710 (21.1)	< 0.001
Gallbladder disease	523 (11.3)	174 (13.8)	349 (10.4)	0.002
Gallbladder polyps, n (%)	369 (8.0)	119 (9.4)	250 (7.4)	0.032
Gallstones, n (%)	151 (3.3)	54 (4.3)	97 (2.9)	0.02
Adenomyomatosis, n (%)	17 (0.4)	6 (0.5)	11 (0.3)	0.597

CRN, colorectal neoplasia.

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

Diseases	No. of subjects	CRN (%)	*P* value	Age < 50 group (n = 2,854)				Age ≥ 50 group (n = 1,772)			
				Subjects, No.	CRN (%)	OR (95% CI)	*P* value	Subjects, No.	CRN (%)	OR (95% CI)	*P* value
Normal gallbladder	4,103	1,084 (26.4)		2,554	499 (19.5)			1,549	585 (37.8)		
Gallbladder disease	523	174 (33.2)	0.002	300	72 (24.0)	1.3 (0.98-1.72)	0.068	223	102 (45.7)	1.39 (1.05-1.84)	0.022
Gallbladder polyp	369	119 (32.2)	0.032	237	57 (24.1)	1.29 (0.94-1.77)	0.104	132	62 (47.0)	1.43 (1.01-2.05)	0.044
Gallstones	151	54 (35.8)	0.02	59	14 (23.7)	1.25 (0.68-2.29)	0.47	92	40 (43.5)	1.23 (0.8-1.87)	0.341
Adenomyomatosis	17	6 (35.2)	0.597	10	3 (30)	1.71 (0.44-6.66)	0.429	7	3 (42.9)	1.18 (0.26-5.31)	0.824

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

and gallbladder disease in 523 (11.3%). One or more gallbladder polyps were detected in 369 (8.0%) and one or more gallstones in 151 (3.3%) participants. The frequency of gallbladder polyp was 8.3% (300/2,854) in patients age < 50 yr and 7.4% (132/1,772) in patients aged ≥ 50 yr. A gallbladder polyp and gallstones were detected in 14 patients. Adenomyomatosis of the gallbladder was detected in 17 patients (0.4%). None of the participants had gallbladder cancer. One or more CRNs were detected in 1,258 patients (27.2%). Among the patients with CRN, 253 patients (5.5%) had one or more advanced CRNs.

There were statistically significant differences in age, sex, smoking, alcohol consumption, presence of abdominal obesity and metabolic syndrome, glucose intolerance or type II diabetes, and hypertriglyceridemia between patients with and without CRNs. Gallbladder diseases were more prevalent in the CRN (+) group than in the CRN (-) group (13.8% vs. 10.4%, $P = 0.002$). The prevalence of gallbladder polyps or gallstones was higher in the CRN (+) group than in the CRN (-) group (9.4% vs. 7.4%, $P = 0.032$; 4.3% vs. 2.9%, $P = 0.020$).

Prevalence of CRN according to gallbladder disease status

The prevalence of CRNs in patients with gallbladder disease was significantly higher than in patients with a normal gallbladder: 33.2% (174/523) vs. 26.4% (1,084/4,103) ($P = 0.002$). The prevalence of CRN 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.

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

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

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	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.

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

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 ≥ 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 cholesterolosis 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 ≥ 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 ≥ 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 ≥ 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% (741/4,187) 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.

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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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REFERENCES

1. Atkin WS, Morson BC, Cuzick J. *Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med 1992; 326: 658-62.*
2. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF, et al. *Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993; 329: 1977-81.*
3. Giovannucci E, Colditz GA, Stampfer MJ. *A meta-analysis of cholecystectomy and risk of colorectal cancer. Gastroenterology 1993; 105: 130-41.*
4. Goldbohm RA, van den Brandt PA, van 't Veer P, Dorant E, Sturmans F, Hermus RJ. *Cholecystectomy and colorectal cancer: evidence from a cohort study on diet and cancer. Int J Cancer 1993; 53: 735-9.*
5. Lagergren J, Ye W, Ekbom A. *Intestinal cancer after cholecystectomy: is bile involved in carcinogenesis? Gastroenterology 2001; 121: 542-7.*
6. Reid FD, Mercer PM, harrison M, Bates T. *Cholecystectomy as a risk factor for colorectal cancer: a meta-analysis. Scand J Gastroenterol 1996; 31: 160-9.*
7. Schernhammer ES, Leitzmann MF, Michaud DS, Speizer FE, Giovannucci E, Colditz GA, Fuchs CS. *Cholecystectomy and the risk for developing colorectal cancer and distal colorectal adenomas. Br J Cancer 2003; 88: 79-83.*
8. Yamaji Y, Okamoto M, Yoshida H, Kawabe T, Wada R, Mitsushima T, Omata M. *Cholelithiasis is a risk factor for colorectal adenoma. Am J Gastroenterol 2008; 103: 2847-52.*
9. Jeun JW, Cha JM, Lee JI, Joo KR, Shin HP, Lim JU. *Association of gallbladder polyp with the risk of colorectal adenoma. Intest Res 2014; 12: 48-52.*
10. Nogueira L, Freedman ND, Engels EA, Warren JL, Castro F, Koshiol J. *Gallstones, cholecystectomy, and risk of digestive system cancers. Am J Epidemiol 2014; 179: 731-9.*
11. Chiong C, Cox MR, Eslick GD. *Gallstones are associated with colonic adenoma: a meta-analysis. World J Surg 2012; 36: 2202-9.*
12. Kahn HS, Tatham LM, Thun MJ, Heath CW Jr. *Risk factors for self-reported colon polyps. J Gen Intern Med 1998; 13: 303-10.*
13. Kim JH, Lim YJ, Kim YH, Sung IK, Shim SG, Oh SO, Park SS, Yang S, Son HJ, Rhee PL, et al. *Is metabolic syndrome a risk factor for colorectal adenoma? Cancer Epidemiol Biomarkers Prev 2007; 16: 1543-6.*
14. Lim SH, Kim DH, Park MJ, Kim YS, Kim CH, Yim JY, Cho KR, Kim SS, Choi SH, Kim N, et al. *Is Metabolic Syndrome One of the Risk Factors for Gallbladder Polyps Found by Ultrasonography during Health Screening? Gut Liver 2007; 1: 138-44.*
15. Hong SN, Kim JH, Choe WH, Han HS, Sung IK, Park HS, Shim CS. *Prevalence and risk of colorectal neoplasms in asymptomatic, average-risk screenees 40 to 49 years of age. Gastrointest Endosc 2010; 72: 480-9.*
16. Tilvis RS, Aro J, Strandberg TE, Lempinen M, Miettinen TA. *Lipid composition of bile and gallbladder mucosa in patients with acalculous cholesterolosis. Gastroenterology 1982; 82: 607-15.*
17. Giovannucci E, Michaud D. *The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology 2007; 132: 2208-25.*
18. Das KM, Vecchi M, Sakamaki S. *A shared and unique epitope(s) on human colon, skin, and biliary epithelium detected by a monoclonal antibody. Gastroenterology 1990; 98: 464-9.*
19. Juhl JH, Crummy AB, Kuhlman JE, Paul LW. *Paul and Juhl's essentials of radiologic imaging. 7th ed. Philadelphia, Pa: Lippincott-Raven, 1998.*
20. Lee SY, Park HS, Kim DJ, Han JH, Kim SM, Cho GJ, Kim DY, Kwon HS, Kim SR, Lee CB, et al. *Appropriate waist circumference cutoff points for central obesity in Korean adults. Diabetes Res Clin Pract 2007; 75: 72-80.*

21. Ito H, Hann LE, D'Angelica M, Allen P, Fong Y, Dematteo RP, Klimstra DS, Blumgart LH, Jarnagin WR. *Polypoid lesions of the gallbladder: diagnosis and followup. J Am Coll Surg 2009; 208: 570-5.*
22. Ishikawa O, Ohhigashi H, Imaoka S, Nakaizumi A, Kitamura T, Sasaki Y, Shibata T, Wada A, Iwanaga T. *The difference in malignancy between pedunculated and sessile polypoid lesions of the gallbladder. Am J Gastroenterol 1989; 84: 1386-90.*
23. Ginanni Corradini S, Yamashita G, Nuutinen H, Chernosky A, Williams C, Hays L, Shiffman ML, Walsh RM, Svanvik J, Della Guardia P, et al. *Human gallbladder mucosal function: effects on intraluminal fluid and lipid composition in health and disease. Dig Dis Sci 1998; 43: 335-43.*
24. Klass DM, Bührmann K, Sauter G, Del Puppo M, Scheibner J, Fuchs M, Stange EF. *Biliary lipids, cholesterol and bile synthesis: different adaptive mechanisms to dietary cholesterol in lean and obese subjects. Aliment Pharmacol Ther 2006; 23: 895-905.*
25. Hubbard B, Doege H, Punreddy S, Wu H, Huang X, Kaushik VK, Mozell RL, Byrnes JJ, Stricker-Krongrad A, Chou CJ, et al. *Mice deleted for fatty acid transport protein 5 have defective bile acid conjugation and are protected from obesity. Gastroenterology 2006; 130: 1259-69.*
26. Park EJ, Lee HS, Lee SH, Chun HJ, Kim SY, Choi YK, Ryu HJ, Shim KW. *Association between metabolic syndrome and gallbladder polyps in healthy Korean adults. J Korean Med Sci 2013; 28: 876-80.*
27. Lee YJ, Park KS, Cho KB, Kim ES, Jang BK, Chung WJ, Hwang JS. *Shifting Prevalence of Gallbladder Polyps in Korea. J Korean Med Sci 2014; 29: 1247-52.*
28. Segawa K, Arisawa T, Niwa Y, Suzuki T, Tsukamoto Y, Goto H, Hamajima E, Shimodaira M, Ohmiya N. *Prevalence of gallbladder polyps among apparently healthy Japanese: ultrasonographic study. Am J Gastroenterol 1992; 87: 630-3.*
29. Chen CY, Lu CL, Chang FY, Lee SD. *Risk factors for gallbladder polyps in the Chinese population. Am J Gastroenterol 1997; 92: 2066-8.*
30. Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, Tjønneland A, Halkjaer J, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, et al. *Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Natl Cancer Inst 2006; 98: 920-31.*
31. Kang HW, Kim D, Kim HJ, Kim CH, Kim YS, Park MJ, Kim JS, Cho SH, Sung MW, Jung HC, et al. *Visceral obesity and insulin resistance as risk factors for colorectal adenoma: a cross-sectional, case-control study. Am J Gastroenterol 2010; 105: 178-87.*
32. Giovannucci E. *Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. Am J Clin Nutr 2007; 86: s836-42.*
33. Wei EK, Ma J, Pollak MN, Rifai N, Fuchs CS, Hankinson SE, Giovannucci E. *A prospective study of C-peptide, insulin-like growth factor-I, insulin-like growth factor binding protein-1, and the risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev 2005; 14: 850-5.*
34. Giovannucci E. *Insulin and colon cancer. Cancer Causes Control 1995; 6: 164-79.*
35. Schmidt M, Småstuen MC, Søndenaa K. *Increased cancer incidence in some gallstone diseases, and equivocal effect of cholecystectomy: a long-term analysis of cancer and mortality. Scand J Gastroenterol 2012; 47: 1467-74.*
36. Collett JA, Allan RB, Chisholm RJ, Wilson IR, Burt MJ, Chapman BA. *Gallbladder polyps: prospective study. J Ultrasound Med 1998; 17: 207-11.*
37. Kim SY, Lee HS, Lee YS, Chung KW, Jang BK, Chung WJ, Park KS, Cho KB, Hwang JS. *Prevalence and risk factors of gallbladder polyp in adults living in Daegu and Gyeongbuk provinces. Korean J Gastroenterol 2006; 48: 344-50.*
38. Okamoto M, Yamagata Z, Takeda Y, Yoda Y, Kobayashi K, Fujino MA. *The relationship between gallbladder disease and smoking and drinking habits in middle-aged Japanese. J Gastroenterol 2002; 37: 455-62.*
39. Lee JK, Rhee PL, Lee JH, Lee KT, Choi SH, Noh JH, Kim JJ, Ko KC, Paik SW, Rhee JC. *Prevalence and risk factors of gallstone in health screening people. Korean J Gastroenterol 1997; 29: 85-92.*
40. Liu CM, Tung TH, Chou P, Chen VT, Hsu CT, Chien WS, Lin YT, Lu HF, Shih HC, Liu JH. *Clinical correlation of gallstone disease in a Chinese population in Taiwan: experience at Cheng Hsin General Hospital. World J Gastroenterol 2006; 12: 1281-6.*

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