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Cholecystectomy and the risk of colorectal cancer by tumor mismatch repair deficiency status

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DISCLAIMER

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DISCLOSURE

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Abstract

Purpose: Gallbladder diseases and cholecystectomy may play a role in the development of colorectal cancer (CRC). Our aim was to investigate the association between cholecystectomy and CRC risk overall and by sex, family history, anatomical location, and tumor mismatch repair (MMR) status.

Methods: This study comprised 5,847 incident CRC cases recruited from population cancer registries in Australia, Canada and USA into the Colon Cancer Family Registry between 1997 and 2012, and 4,970 controls with no personal history of CRC who were either randomly selected from the general population or were spouses of the cases. The association between cholecystectomy and CRC was estimated using logistic regression, after adjusting for confounding factors.

Results: Overall, there was no evidence for an association between cholecystectomy and CRC (odds ratio [OR] = 0.88, 95% confidence interval: 0.73, 1.08). In the stratified analyses, there was no evidence for a difference in the association between women and men (*P*=.54), between individuals with and without family history of CRC in first-degree relative (*P*=.64), between tumor anatomical locations (*P*=.45), or between MMR-proficient and MMR-deficient cases (*P*=.54).

Conclusion: Cholecystectomy is not a substantial risk factor for CRC, regardless of sex, family history, anatomical location, or tumor MMR status.

Introduction

Colorectal cancer (CRC) accounts for 10% of all cancer incidence and is the fourth ranking cause of cancer mortality worldwide [1]. In 2012, 746,000 men and 614,000 women were diagnosed with CRC globally, with highly industrialized and urbanized societies (including North America, most European countries, Japan and Australia) contributing to more than half. Identifying risk factors associated with CRC may inform strategies to prevent and detect cancers at an early stage. Certain medical conditions and interventions may play a role in the development of CRC [2].

Gallbladder diseases such as gallstones which lead to gallbladder inflammation (cholecystitis) are highly prevalent in Western populations [3,4]. The lifetime risk of developing gallstones in Western populations is between 5% and 25% and women in the US under 40 years of age are at nearly twice the risk of developing gallstones than men[5]. The common treatment for inflammatory gallstones, cholecystectomy, has the potential to lead to increased bile exposure in the colon and rectum. Bile acids cause DNA damage probably indirectly through the induction of oxidative stress and the production of reactive oxygen species. Excessive DNA damage may cause genetic instability and increase mutations of tumor suppressor genes and oncogenes, subsequently increasing the risk of CRC [6].

Previous studies have reported conflicting results on associations between gallstones and/or cholecystectomy and CRC [7,8] or colorectal adenoma [9]. Further, risks may be differentially associated with cancer at different anatomical locations within the colon [10]. No previous studies have examined the association between cholecystectomy and CRC according to their tumor mismatch repair (MMR) status.

Here, we investigated associations between cholecystectomy and CRC risk by sex, family history, anatomical location and tumor MMR status.

Materials and Methods

Study Sample

This study was designed as a retrospective case-control study. Cases were individuals diagnosed with incident colon or rectal cancer who were recruited through population cancer registries from four centers of the Colon Cancer Family Registry between 1997 and 2012, Cancer Care Ontario (Toronto, Canada), Fred Hutchinson Cancer Research Center (Seattle, US), Mayo Clinic (Rochester, US), and The University of Melbourne (Melbourne, Australia) [11]. We only included cases interviewed by staff from the Colon Cancer Family Registry within 5 years of diagnosis. Controls were either individuals with no personal history of CRC who were recruited randomly from the general population through Medicare and Driver's License files, telephone subscribers lists, electoral rolls, or the CRC cases' spouses with no personal history of CRC. For all participants, we excluded those without information on whether or not they had cholecystectomy.

Data Collection

We collected data on demographic information, personal and familial history of CRC, medical history including surgeries, medical conditions and drug use, alcohol intake, smoking status for all participants and reproductive history for women at the time of baseline recruitment. Uniform questionnaires (http://coloncfr.org/questionnaires) were used to acquire data by telephone interviews (Fred Hutchinson Cancer Research Center, University of Melbourne and Mayo Clinic) and mails (Cancer Care Ontario

and Mayo Clinic). All participants were asked whether or not they had surgical removal of their gallbladder and if so, at what age they were at the time of the removal.

Tumor molecular characterization

CRCs were characterized for MMR-deficiency by microsatellite instability (MSI) using a ten-marker panel (four mononucleotide markers (BAT25, BAT26, BAT40, and BAT34C4), five dinucleotide markers (D5S346, D17S250, ACTC, D18S55, and D10S197), and one penta-mono-tetra compound-repeat marker (MYCL)) and/or by immunohistochemistry (IHC) for the four MMR proteins. Tumors were classified as MMR-deficient if they were MSI-high (≥30% unstable markers) and/ or showed loss of expression of one or more of the MMR proteins by IHC; and MMR-proficient if they were microsatellite stable (no unstable markers) or MSI-low (<30% unstable markers) and/or showed normal expression of all four MMR proteins by IHC [11].

Statistical Analysis

Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the association between cholecystectomy and CRC were estimated using multivariable unconditional logistic regression. We estimated the associations stratified by sex, first-degree family history, anatomical location, and tumor MMR status. We investigated potential interactions between cholecystectomy status and age at study recruitment (≤45, 45-55, 55-65 and >65 years), sex, recent BMI and BMI at age 20 years (underweight, normal, overweight and obese) using likelihood ratio tests comparing the results with and without the interaction terms in the logistic regression models.

To investigate whether the time since cholecystectomy was associated with CRC risk for the participants that had undergone cholecystectomy, we compared the mean of time since cholecystectomy between cases (age at CRC diagnosis minus age at cholecystectomy) and controls (age at study recruitment minus age at cholecystectomy) using a multivariable linear regression model.

Some centers of the Colon Cancer Family Registry used stratified sampling based on family history for recruitment, and we did take this into account when combining and analyzing the data. To adjust for the stratified sampling, we gave each individual a probability weight equal to the reciprocal of the family sampling fraction. All statistical analyses were conducted using STATA version 13.0 (StataCorp, College Station, TX).

Results

This study comprised 5,847 pathologically confirmed CRC cases, and 4,243 population-based controls and 727 spouse-controls (**Figure 1**). Baseline characteristics of cases and controls are presented in **Table 1**.

In total, 521 (8.9%) cases and 555 (11.2%) controls had undergone cholecystectomy. Overall, there was no evidence for an association between cholecystectomy and CRC (OR=0.88, 95% CI: 0.73, 1.08) after adjusting for confounding factors. In stratified analyses, there was no evidence for a difference in the association between women and men (*P*=.54), between individuals with and without a family history of CRC in first-degree relative (*P*=.64), between tumor anatomical locations (*P*=0.45), or between MMR-proficient and MMR-deficient cases (*P*=.54) (**Table 2**). There was no

evidence for interactions between cholecystectomy status and age at study recruitment, sex, recent BMI and BMI at age 20 years (details not shown).

Moreover, there was no evidence for a difference in the time since cholecystectomy between cases and controls (14.5 (SD 12.1) years vs. 15 (SD 11.6) years; mean difference: -0.0003, 95%CI: -0.004, 0.003 years, *P*=.86), after adjusting for confounding factors.

Discussion

We found no evidence for an association between cholecystectomy and CRC risk, overall or by sex, first-degree family history of CRC, anatomical location or tumor MMR status. This study is the first to examine the association according to tumor MMR status.

Although a few studies have reported a positive association between cholecystectomy and CRC risk [12] [13], previous meta-analyses have reported that cholecystectomy was not associated with the risk of proximal colon cancer [7], rectal cancer [8] or colorectal adenoma [9]. However, most of the previous studies adjusted only for age and sex [10]. In our current study, we adequately adjusted for additional important confounding factors such as obesity, diabetes, and family history.

The strengths of our study include large sample size and high quality data of the Colon Cancer Family Registry, which employs standardized protocols for data and biospecimens collection [11]. One limitation of our study is the possibility of recall bias because cholecystectomy information was self-reported and not validated by medical records. However, a previous study reported 99.6% agreement between self-report and medical records for cholecystectomy [14]. Further, given approximately

90% of our study participants are Caucasians from developed countries, the study results may not be applicable to other populations.

In conclusion, our findings suggest that cholecystectomy is not a substantial risk factor for CRC, regardless of sex, family history, anatomical location, or tumor MMR status.

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Figure Legend

Figure 1. Selection of colorectal cancer cases and controls from the Colon Cancer Family Registry

Table 1. Baseline characteristics of colorectal cancer cases and controls

Variables	**Cases, N (%)** (n = 5847)	**Controls, N (%)** Total controls (n = 4970)	Population controls (n = 4243)	Spouse controls (n =727)
Age at recruitment, years				
Mean (SD)	55.2 (11.8)	57.5 (11.6)	58.4 (11.7)	52.5 (10)
Median (range)	54	59	60	52
Sex				
Female	2959 (50.6)	2630 (52.9)	2191 (51.6)	439 (60.4)
Male	2888 (49.4)	2340 (47.1)	2052 (48.4)	288 (39.6)
Recruitment centre				
Cancer Care Ontario	2098 (35.9)	1920 (38.6)	1920 (45.2)	0
University of Melbourne	807 (13.8)	719 (14.5)	270 (6.4)	449 (61.8)
Mayo Clinic	623 (10.7)	278 (5.6)	0	278 (38.2)
Fred Hutchinson Seattle	2319 (39.6)	2053 (41.3)	2053 (48.4)	0
Cholecystectomy				
Yes	521 (8.9)	555 (11.2)	504 (11.9)	51 (7)
No	5326 (91.1)	4415 (88.8)	3739 (88.1)	676 (93)
Family history of CRC (first-degree relative)				
Yes (at least 1 affected)	1248 (21.3)	529 (10.6)	460 (10.8)	69 (9.5)
No	4599 (78.7)	4441 (89.4)	3783 (89.2)	658 (90.5)
Body mass index, recent (kg/m^2)				
Underweight (<18.5)	86 (1.5)	57 (1.2)	50 (1.2)	7 (1)
Normal (18.5-24.9)	2010 (34.4)	2020 (40.6)	1732 (40.8)	288 (39.6)
Overweight (25.0-29.9)	2214 (37.9)	1849 (37.2)	1626 (38.3)	223 (30.7)
Obese (≥30)	1413 (24.2)	922 (18.5)	789 (18.6)	133 (18.3)
Missing	124 (2)	122 (2.5)	46 (1.1)	76 (10.4)
Body mass index at age 20 years (kg/m^2)				
Underweight (<18.5)	423 (7.2)	439 (8.8)	373 (8.8)	66 (9.1)
Normal (18.5-24.9)	3989 (68.2)	3595 (72.3)	3121 (73.6)	474 (65.2)
Overweight (25.0-29.9)	969 (16.6)	638 (12.8)	549 (12.9)	89 (12.2)
Obese (≥30)	230 (3.9)	112 (2.3)	95 (2.2)	17 (2.3)
Missing	236 (4.1)	186 (3.8)	105 (2.5)	81 (11.2)
Cigarette smoking				
Current^^	662 (11.3)	638 (12.8)	537 (12.7)	101 (13.9)
Former^	2635 (45.1)	2056 (41.4)	1788 (42.1)	268 (36.9)
Never	2511 (43)	2250 (45.3)	1901 (44.8)	349 (48)
Missing	39 (0.6)	256 (0.5)	17 (0.4)	9 (1.2)
Education				
Primary school	107 (1.8)	91 (1.8)	79 (1.9)	12 (1.6)
Secondary school	821 (14)	658 (13.2)	541 (12.7)	117 (16.1)
High/Senior secondary school	1310 (22.4)	958 (19.3)	789 (18.6)	169 (23.3)
Vocational education or training	583 (10)	466 (9.4)	352 (8.3)	114 (15.7)
University without degree	1330 (22.8)	1089 (21.9)	1025 (24.2)	64 (8.8)

University graduation or higher	1649 (28.2)	1618 (3.6)	1444 (34)	174 (23.9)
Missing	47 (0.8)	90 (1.8)	13 (0.3)	77 (10.6)
Annual household Income				
≤ $15,000	319 (5.5)	190 (3.8)	186 (4.4)	4 (0.5)
$15,000-30,000	777 (13.3)	572 (11.5)	538 (12.7)	34 (4.7)
$30,000-45,000	1031 (17.6)	925 (18.6)	864 (20.4)	61 (8.4)
$45,000-70,000	1068 (18.3)	933 (18.8)	870 (20.5)	63 (8.6)
≥ $70,000	1026 (17.5)	876 (17.6)	790 (18.6)	86 (11.8)
Refused to answer	144 (2.5)	147 (3)	140 (3.3)	7 (1)
Missing	1482 (25.3)	1327 (26.7)	855 (20.1)	472 (64.9)
Race				
Caucasian	5206 89)	4592 (92.4)	3944 (93)	648 (89.1)
Other	514 (8.8)	276 (5.6)	254 (6)	22 (3)
Missing	127 (2.2)	102 (2)	45 (1)	57 (7.9)
Diabetes mellitus				
Yes	468 (8)	376 (7.6)	340 (8)	36 (5)
No	5360 (91.7)	4581 (92.2)	3895 (91.8)	686 (94.3)
Missing	19 (0.3)	13 (0.2)	8 (0.2)	5 (0.7)
Aspirin intake**				
≥5years	471 (8.1)	623 (12.5)	577 (13.6)	46 (6.3)
<5years	884 (15.1)	888 (17.9)	806 (19)	82 (11.3)
Never	4231 (72.4)	3263 (65.7)	2705 63.8)	558 (76.8)
Missing	261 (4.4)	196 (3.9)	155 (3.7)	41 (5.6)
Ibuprofen intake**				
≥5years	172 (3)	182 (3.7)	155 (3.7)	27 (3.7)
<5years	685 (11.7)	719 (14.5)	642 (15.1)	77 (10.6)
Never	4756 (81.3)	3904 (78.5)	3332 (78.5)	572 (78.7)
Missing	234 (4)	165 (3.3)	114 (2.7)	51 (7)
Multivitamin intake**				
≥5years	1553 (26.6)	1463 (29.4)	1361 (32.1)	102 (14)
<5years	1102 18.8)	859 (17.3)	752 (17.7)	107 (14.7)
Never	2845 (48.7)	2434 (49)	1975 (46.5)	459 (63.2)
Missing	347 (5.9)	214 (4.3)	155 (3.7)	59 (8.1)
Regular physical activity*				
Yes	5023 (85.9)	4287 (86.3)	3668 (86.5)	619 (85.1)
No	90 (1.5)	108 (2.2)	89 (2.1)	19 (2.6)
Missing	734 (12.6)	575 (11.5)	486 (11.4)	89 (12.2)
Alcohol consumption (standard drink per day) ^^^				
Mean (SD)	1.2 (2.3)	1 (2.1)	1.1 (2.1)	0.9 (1.6)
Missing, N	1684	1225	1075	150
Red meat consumption (number of serve per day)				
Mean (SD)	0.66 (0.63)	0.58 (0.55)	0.54 (0.53)	0.81 (0.66)
Missing, N	187	222	149	73
Number of live birth #				

0	374 (12.6)	269 (10.2)	230 (10.5)	39 (8.9)
1	349 (11.8)	275 (10.4)	230 (10.5)	45 (10.3)
2	909 (30.7)	830 (31.6)	656 (29.9)	174 (39.6)
3	605 (20.5)	538 (20.5)	440 (20.1)	98 (22.3)
≥4	516 (17.4)	412 (15.7)	345 (15.8)	67 (15.3)
Missing	206 (7)	306 (11.6)	290 (13.2)	16 (3.6)
Hormonal contraceptives[#]				
≥5 years	1007 (34)	939 (35.7)	719 (32.8)	220 (50.1)
<5 years	577 (19.5)	545 (20.7)	433 (19.8)	112 (25.5)
Never	1192 (40.3)	1023 (38.9)	935 (42.7)	88 (20.1)
Missing	183 (6.2)	123 (4.7)	104 (4.7)	19 (4.3)
Hormone replacement therapy[#]				
Estrogen-only users	491 (16.6)	473 (18)	411 (18.8)	62 (14.1)
Progesterone and estrogen users	187 (6.3)	214 (8.1)	187 (8.5)	27 (6.2)
Never	1879 (63.5)	1467 (55.8)	1221 (55.7)	246 (56)
Missing	402 (13.6)	476 (18.1)	372 (17)	104 (23.7)
Anatomical location				
Proximal colon	1968 (33.6)	—	—	—
Distal colon	1811 (31)	—	—	—
Colon unspecified	81 (1.4)	—	—	—
Rectum	1987 (34)	—	—	—
Tumor MMR status				
MMR-proficient tumor	3790 (64.8)	—	—	—
MMR-deficient tumor	631 (10.8)	—	—	—
Missing	1426 (24.4)	—	—	—

[#] Questions asked only for women (2959 cases and 2630 controls)

[*] regular physical activity defined as any physical activity for at least 30 minutes per week for at least 3 months

[**] at least twice a week for at least 1 month

^ former smokers defined as participants who had smoked at least 1 cigarette per day for at least 3 months and had quit more than 2 years before age at colorectal cancer or age at interview.

^^ current smokers defined as participants who had smoked at least 1 cigarette per day for at least 3 months and continued within 2 years of age at colorectal cancer or age at interview.

^^^4-oz. glasses of wine, or 12-oz. cans or bottles of beer or hard cider, or 1-oz. servings of sake or liquor (spirits)

MMR, mismatch repair; SD, standard deviation; N, number; __, not relevant

Table 2. Association between cholecystectomy and the risk of colorectal cancer overall and stratified by sex, family history, anatomical location and tumor mismatch repair status

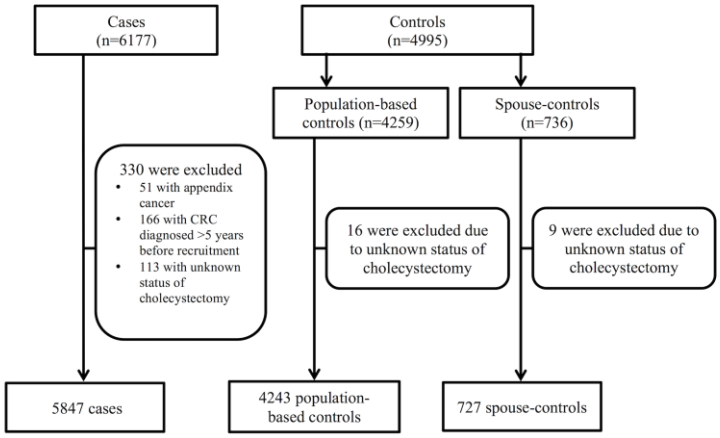
	Cases	Controls	Unadjusted		Adjusted**		
	n/N	n/N	OR (95% CI)	P-value	OR (95% CI)	P-value	P-difference*
Overall	521/5847	555/4970	0.76 (0.66, 0.88)	.001	0.88 (0.73, 1.08)	.22	
Sex							
Women[b]	395/2959	410/2630	0.84 (0.72, 0.99)	.04	1.00 (0.78, 1.28)	.99	.54
Men	126/2888	145/2340	0.74 (0.56, 0.97)	.03	0.78 (0.53, 1.13)	.19	
Family history		555/4970					
No	399/4599		0.75 (0.65, 0.88)	<.001	0.86 (0.69, 1.06)	.16	
Yes	122/1248		0.90 (0.71, 1.14)	.39	0.98 (0.71, 1.33)	.88	.64
Anatomical location		555/4970					
Proximal colon	216/1968		1.02 (0.42, 1.23)	.83	0.93 (0.70, 1.24)	.63	.45
Distal colon	151/1811		0.70 (0.56, 0.86)	.001	0.75 (0.56, 1.02)	.07	
Colon unspecified	3/81		0.30 (0.09, 0.95)	.04	0.59 (0.13, 2.63)	.49	
Rectum	151/1987		0.66 (0.53, 0.82)	<.001	0.97 (0.72, 1.29)	.84	
Tumor MMR status		555/4970					
Proficient	314/3790		0.74 (0.63, 0.87)	<.001	0.86 (0.68, 1.09)	.20	.54
Deficient	71/631		0.99 (0.73, 1.34)	.93	0.96 (0.63, 1.49)	.87	

OR, Odds ratio; CI, confidence interval, MMR, mismatch repair; n, number of individuals with cholecystectomy; N, total number

* for stratified analysis by sex: it was calculated using likelihood ratio tests on unconditional multivariable logistic regression models; for stratified analyses by first-degree family history, anatomical location and tumor MMR status, it was calculated using likelihood ratio tests on multinomial logistic regression models.

** adjusted for sex (women or men, except for stratified analysis by sex), first-degree family history (no, yes; except for stratified analysis by family history), age at study recruitment (continuous), alcohol consumption (per standard drink per day), BMI (WHO categories), BMI at age 20 years (WHO categories), cigarette smoking (never, former, current), aspirin (non-users, <5 years use, ≥5 years use), ibuprofen (non-users, <5 years use, ≥5 years use), diabetes status (no, yes), recruitment center (Cancer Care Ontario, Fred Hutchinson Cancer Research Center, Mayo Clinic or University of Melbourne), regular physical activity (no, yes), and red meat consumption (serving per day)

[b] For women, further adjusted for hormonal contraceptive use (non-users, <5 years use, ≥5 years use) and number of live birth (never, 1, 2, 3, ≥4)


Cases
(n=6177)
Controls
(n=4995)
Population-based
controls (n=4259)
Spouse-controls
(n=736)
330 were excluded
51 with appendix cancer
166 with CRC diagnosed >5 years before recruitment
113 with unknown status of cholecystectomy
16 were excluded due to unknown status of cholecystectomy
9 were excluded due to unknown status of cholecystectomy
5847 cases
4243 population-based controls
727 spouse-controls