Appendectomy and Future Risk of Microscopic Colitis: A Population-Based Case-Control Study in Sweden

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BACKGROUND AND AIMS: **Microscopic colitis (MC) is an inflammatory bowel disease and a common cause of chronic diarrhea. Appendectomy has been suggested to have immunomodulating effects in the colon, influencing the risk of gastrointestinal disease. The relationship between appendectomy and MC has only been sparsely studied.**

METHODS: **This was a case-control study based on the nationwide ESPRESSO (Epidemiology Strengthened by histoPathology Reports in Sweden) cohort, consisting of histopathological examinations in Sweden, linked to national registers. Patients with MC were matched to population controls by age, sex, calendar year of biopsy, and county of residence. Data on antecedent appendectomy and comorbidities were retrieved from the Patient Register. Unconditional logistic regression models were conducted presenting odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for country of birth and matching factors. Further subanalyses were made based on MC subtypes (lymphocytic colitis and collagenous colitis), follow-up time postappendectomy and severity of appendicitis.**

RESULTS: **The study included 14,520 cases of MC and 69,491 controls, among these 7.6% (n = 1103) and 5.1% (n = 3510), respectively, had a previous appendectomy ≥1 year prior to MC or matching date. Patients with a previous appendectomy had an increased risk of MC in total (OR, 1.50; 95% CI, 1.40–1.61) and per the collagenous colitis subtype (OR, 1.67; 95% CI, 1.48–1.88) or lymphocytic colitis subtype (OR, 1.42; 95% CI, 1.30–1.55). The risk remained elevated throughout follow-up, and the highest risk was observed in noncomplicated appendicitis.**

CONCLUSIONS: **This nationwide case-control study found a modestly increased risk of developing MC following appendectomy.**

Keywords: Appendicitis; Surgery; Laparoscopy; Microscopic Colitis; Gastrointestinal; Population Based.

Microscopic colitis (MC) is an inflammatory bowel disease (IBD) and accounts for up to 20% of cases of chronic diarrhea among individuals >65 years of age, with an incidence similar to other IBD subtypes.[1] A cohort study estimated MC to affect 1 in 115 women and 1 in 286 men.[2] However, the causes of MC remains to be further elucidated.[1,3] Appendectomy has been suggested to cause immunomodulating effects in the colon, and earlier studies have shown an inverse relationship between appendectomy and ulcerative colitis,[4–9] and celiac disease.[10] Data on appendectomy and the risk of developing Crohn's disease are less consistent.[11–17] Previous studies have observed that the risk of Crohn's disease is influenced by both time since appendectomy and severity of appendicitis.[16] The relationship between appendectomy and MC has only been examined in 2 previous studies, with limited sample size, both studies

Abbreviations used in this paper: **aOR, adjusted odds ratio; CC, collagenous colitis; CI, confidence interval; IBD, inflammatory bowel disease; LC, lymphocytic colitis; MC, microscopic colitis; OR, odds ratio; Th17, T helper 17.**

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found no association between appendectomy and MC.[18,19]

This study sought to investigate the relation between appendectomy and MC based on a Swedish nationwide cohort.[20] The aim was to study a possible association between MC and antecedent appendectomy, as well as the impact of severity of appendicitis and time between appendectomy and MC, hypothesizing that appendectomy due to appendicitis might increase the risk of MC.

What You Need to Know

Background

Microscopic colitis (MC) is an inflammatory bowel disease and a cause of chronic diarrhea. It has been suggested that appendectomy might lead to immunomodulation of the colon. This study investigated the relationship between appendectomy and MC.

Findings

This nationwide case-control study included 14,520 patients with MC and 69,491 controls. The risk of developing MC was significantly increased after appendectomy.

Implications for patient care

Patients with a history of appendectomy might be at an increased risk of developing MC, albeit the risk of MC following appendectomy was moderately increased.

Materials and Methods

Cohort Description

The ESPRESSO (Epidemiology Strengthened by histoPathology Reports in Sweden) cohort is based on histopathology data from the gastrointestinal tract between January 1965 and April 2017.[20] Data included personal identity number, date of biopsy, anatomic location, and morphology based on the SNOMED (Systematized Nomenclature of Medicine) system. Data regarding age, emigration, sex, and county of residence was retrieved from the Swedish Total Population Register.[21] Information on education was collected from the LISA (longitudinal integrated database for health insurance and labor market studies), which includes information from the labor, educational, and social sectors from year 1990. Education data are available in >98% of all individuals, with an estimated accuracy for highest level of education of 85%.[22] Educational level was categorized as compulsory school (≤9 years), upper secondary school (10–12 years), or university (≥13 years). Further data was retrieved from the Swedish Patient Register and Cause of Death Register.[23] The Cause of Death Register contains data on date and causes of death and covers >99% of all deaths.[24] The Swedish Patient Register was founded in 1964 and reached nationwide coverage in 1987. The Swedish Patient Register has shown a high validity with a positive predictive value of 85–95% for most diagnoses.[25] The Swedish Patient Register was used to identify appendectomy using surgical procedure codes between 1965 and 1996, and the Nordic Medico-Statistical Committee system after year 1997 (Supplementary Table 1), and further, it was used to identify patients with a diagnosis of other IBD (Supplementary table 2).

Ascertainment of MC

All adults with a biopsy of MC during 1990–2017 were identified. MC cases diagnosed before 1990 were excluded due to the significantly increased incidence observed 1990, suggesting lower validity prior 1990.[2] Topography codes representing colon (T67) and rectum (T68) were used in combination with SNOMED codes indicating the different subtypes of MC, namely collagenous colitis (CC) (M40600) and lymphocytic colitis (LC) (M47170). Cases were categorized as MC overall and the 2 subtypes (CC and LC).[26] The first biopsy (index biopsy), defined date of diagnosis with MC. A validation study that identified MC cases through histopathology registers in Sweden showed this methodology to yield a positive predictive value of 95% among patients for a clinical diagnosis of MC (95% for CC and 85% for LC).[27]

Control Population

Each case was matched to 5 controls from the general population with no prior diagnosis of MC at date of index biopsy. The matching was conducted by the government agency Statistics Sweden using the matching factors: exact age at matching date, sex, calendar year of case index biopsy, and county of residence.

Exclusions

Subjects formally emigrated prior to index biopsy date demonstrating MC, or matching date, were excluded due to poor coverage regarding appendectomy.

Exposure Ascertainments

The exposure was previous appendectomy, defined as appendectomy at least 1 year prior index biopsy demonstrating MC, or matching date in controls. Appendectomy was identified using surgical procedure codes and the NOMESCO (Nordic Medico-Statistical Committee) system. The nomenclature defining complicated and noncomplicated appendicitis is not standardized[28,29]; therefore, complicated and noncomplicated appendicitis was defined with surgical procedure codes in combination with the International Classification of

Diseases (seventh to tenth revisions) codes (Supplementary Table 3).

Statistical Analysis

This was a population-based, case-control study comparing MC cases including per subtype with controls from the general population. Adjusted unconditional logistic regression was conducted presenting odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for country of birth and matching variables (age, sex, calendar year of biopsy, and county of residence).[30] First, calculations of aORs and 95% CI was conducted based on years since appendectomy to diagnosis with MC, overall ($\geq$1 year) as well as categorized (1–<5, 5–10, and >10 years). Second, 2 subgroup analyses were conducted. The first was based on severity of appendicitis (incidental appendectomy, noncomplicated appendicitis, and complicated appendicitis), stratified by time since appendectomy. The second subgroup analysis conducted included patients who received a diagnosis of MC <1 year after appendectomy, to determine if a potential misclassification of MC involving the appendix could influence the results.

Sensitivity Analysis

One sensitivity analysis was conducted excluding patients with another IBD diagnosis before index biopsy with MC or the matching date in controls, among both cases and controls. Four post hoc sensitivity analyses were further conducted. One assessed the risk of MC following appendectomy among MC cases and controls, restricting controls to those with a prior history of colonoscopy, and one assessed the risk of MC following appendectomy but in which number of healthcare visits was adjusted for in the regression model, accounting for healthcare utilization. A further 2 additional post hoc analysis were conducted, one comparing patients with a history of open umbilical hernia and one comparing patients with a history of knee arthroscopy. The 2 latter sensitivity analyses were conducted to assess potential residual confounding.

Ethics

The study was approved by the Stockholm Ethics Review Board (No. 2014/1287-31/4 and 2018/972-32). The study was register based, and informed consent was therefore waived.

Results

Characteristics

In the cohort, 14,520 cases of MC (4684 CC and 9836 LC) were matched to 69,491 controls (Table 1). Most cases (43.2%) were diagnosed between 50 and 70 years of age, having their index biopsy between 2005 and 2012, and women accounted for 71.8%. The patients diagnosed with MC were more likely to have been born in a Nordic country compared with controls. Level of education was equally distributed, with 9–12 years of education as most common. Prior diagnosis with another IBD was prevalent in 4.3% of all cases. Previous appendectomy was prevalent among 7.6% of all cases compared with 5.1% in controls. Age at appendectomy was most common in the age span >20–$\leq$40 years The dominating severity was noncomplicated appendicitis, incidental appendectomy was the second most common diagnosis, and complicated appendicitis was least prevalent.

Appendectomy and Risk of MC

A total of 1103 (7.6%) of the MC patients had an earlier appendectomy, compared with 3510 (5.1%) of the controls. Appendectomy $\geq$1 year prior to biopsy with MC showed an adjusted OR (aOR) of 1.50 (95% CI, 1.40–1.61) (aORs per subtype: CC, 1.67; 95% CI, 1.48–1.88; and LC, 1.42; 95% C, 1.30–1.55) (Table 2). A sensitivity analysis was conducted excluding patients with another IBD prior to date of diagnosis with MC or matching and showed no effect on the results in any subgroup. In the sensitivity analysis limiting controls to only include patients with previous colonoscopy, the overall aOR was 1.16 (95% CI, 0.98–1.38). Further, in the sensitivity analysis including number of inpatient visits in the model as a proxy for healthcare utilization, the overall aOR was 1.26 (95% CI, 1.18–1.39). In the cohort, there were 174 patients with a history of open umbilical hernia repair, 36 of whom were later diagnosed with MC, and the overall aOR for developing MC was 1.26 (95% CI, 0.87–1.82). Further, there were 1223 patients with a history of knee arthroscopy, 294 of whom were later diagnosed with MC (aOR, 1.48; 95% CI, 1.29–1.69).

In exploratory analyses, the risk of MC overall and per subtype after appendectomy was examined for different time windows (Table 2). Index biopsy <1 year after appendectomy showed the highest associated risk of MC (aOR, 3.17; 95% CI, 2.05–4.91), albeit the risk remained elevated in all time windows. The same time windows were examined among subtypes and showed a similar pattern with the highest risk <1 year since appendectomy.

Severity of Appendicitis and Risk of MC

The association between severity of appendicitis and MC, in total and per subtype, was also investigated over time (Table 3). When examining all cases, the highest associated risk was found <1 year after appendectomy with noncomplicated appendicitis (aOR, 3.36; 95% CI, 2.14–5.26). For incidental appendectomy and

Table 1. Characteristics of Study Population Stratified by Controls, by Microscopic Colitis, and per Subtype

	Controls	Microscopic Colitis	Collagenous Colitis	Lymphocytic Colitis
Number of patients	69,491	14,520	4684	9836
Age at index biopsy				
<50 y	17,276 (24.9)	3502 (24.1)	805 (17.2)	2697 (27.4)
50–70 y	30,679 (44.1)	6276 (43.2)	2125 (45.4)	4151 (42.2)
≥70 y	21,536 (31.0)	4742 (32.7)	1754 (37.4)	2988 (30.4)
Female	50,062 (72.0)	10,428 (71.8)	3592 (76.7)	6836 (69.5)
Calendar year of index biopsy				
≤2004	16,550 (23.8)	3422 (23.6)	1103 (23.5)	2319 (23.6)
2005–2011	29,897 (43.0)	6259 (43.1)	2094 (44.7)	4165 (42.3)
≥2012	23,044 (33.2)	4839 (33.3)	1487 (31.7)	3352 (34.1)
Country of birth (Nordic)	61,682 (88.8)	13,640 (93.9)	4490 (95.9)	9150 (93.0)
Education				
≤9 y	17,947 (25.8)	3827 (26.4)	1443 (30.8)	2384 (24.2)
10–12 y	28,696 (41.3)	5964 (41.1)	1952 (41.7)	4012 (40.8)
≥13 y	22,128 (31.8)	4574 (31.5)	1253 (26.8)	3321 (33.8)
Prior diagnosis of inflammatory bowel disease	320 (0.5)	626 (4.3)	278 (5.9)	348 (3.5)
Appendectomy				
Appendectomy	3510 (5.1)	1103 (7.6)	394 (8.4)	709 (7.2)
Laparoscopic appendectomy[a]	75 (0.1)	46 (0.3)	13 (0.3)	33 (0.3)
Age at appendectomy				
≤20 y	731 (20.8)	226 (20.5)	71 (18.0)	155 (21.9)
>20–≤40 y	1541 (43.9)	473 (42.9)	164 (41.6)	309 (43.6)
>40–≤60 y	1040 (29.6)	324 (29.4)	123 (31.2)	201 (28.3)
>60 y	198 (5.6)	80 (7.3)	36 (9.1)	44 (6.2)
Diagnosis of appendix				
Incidental appendectomy[b]	981 (27.9)	262 (23.8)	113 (28.7)	149 (21.0)
Noncomplicated appendicitis	1897 (54.0)	669 (60.7)	211 (53.6)	458 (64.6)
Complicated appendicitis	632 (18.0)	172 (16.5)	70 (17.8)	102 (14.4)

Values are n or n (%).
[a]Also included in the overall group "appendectomy."
[b]Appendectomy "en passant."

appendectomy due to complicated appendicitis in MC cases overall, the highest risk was seen after 5–10 years.

In CC cases, the highest risk was observed 5–10 years after incidental appendectomy (aOR, 6.99; 95% CI, 1.97–24.80), and in complicated appendicitis, the highest risk was seen 1–5 years after appendectomy (aOR, 3.85; 95% CI, 0.85–17.46). Among CC patients with noncomplicated appendicitis, the highest risk was found <1 year after appendectomy (aOR, 3.96; 95% CI, 1.77–8.88).

In LC cases, the time period <1 year since appendectomy with noncomplicated appendicitis showed the highest associated risk (aOR, 3.12; 95% CI, 1.82–5.36). In complicated appendicitis, the highest associated risk was seen after 5–10 years (aOR, 2.31; 95% CI, 0.99–5.37), and after incidental appendectomy, the highest risk was observed 5–10 after years (aOR, 2.14; 95% CI, 0.82–5.58).

Discussion

This nationwide case-control study including 14,520 MC cases and 69,491 controls showed an increased risk of MC after appendectomy, lasting beyond 10 years after appendectomy. The risk of MC following antecedent appendectomy remained increased in all follow-up time periods studied, as well as for different severities of appendicitis.

The main strength of this study is the large cohort size and study design, and this is, to our knowledge, the largest study to examine the relation between appendectomy and MC. Furthermore, all MC cases were identified based on histopathology, increasing validity of the inclusion. MC cases and subjects with previous appendectomy were identified using a validated method that has shown a positive predictive value of 95.0% and 90.3%, respectively.[25,27] Furthermore, the observed prevalence of appendicitis of 5.1% in controls and 7.6% in MC cases is in line with the lifetime risk of 8.0%.[31] Previous studies investigating the relation between appendectomy and IBD have observed an influence of age at the time of appendectomy and future risk of IBD.[8,16] Following the main analysis, a post hoc analysis was conducted categorizing the study population by age at appendectomy (≥1 year follow-up after appendectomy in all severities of appendicitis), and this

Table 2. Risk of Microscopic Colitis and per Subtype Following Appendectomy Compared With Controls

Years Since Appendectomy	Controls	Cases	OR (95% CI)	aOR (95% CI)
Microscopic colitis				
<1 (subanalysis)	50	34	3.26 (2.11–5.04)	3.17 (2.05–4.91)
≥1 (overall)	3510	1103	1.55 (1.44–1.66)	1.50 (1.40–1.61)
1–<5	186	74	1.96 (1.49–2.56)	1.97 (1.50–2.58)
5–10	229	111	2.38 (1.90–2.99)	2.37 (1.89–2.98)
>10	3095	918	1.46 (1.35–1.57)	1.41 (1.30–1.52)
Collagenous colitis				
<1 (subanalysis)	14	11	3.73 (1.69–8.21)	3.68 (1.66–8.12)
≥1 (overall)	1122	394	1.72 (1.53–1.94)	1.67 (1.48–1.88)
1–<5	49	20	2.00 (1.19–3.37)	2.00 (1.19–3.38)
5–10	70	36	2.52 (1.69–3.79)	2.52 (1.68–3.77)
>10	1003	338	1.65 (1.46–1.88)	1.60 (1.40–1.81)
Lymphocytic colitis				
<1 (subanalysis)	36	23	3.08 (1.82–5.20)	2.99 (1.77–5.04)
≥1 (overall)	2388	709	1.46 (1.34–1.59)	1.42 (1.30–1.55)
1–<5	137	54	1.94 (1.41–2.66)	1.95 (1.42–2.68)
5–10	159	75	2.32 (1.76–3.06)	2.30 (1.75–3.04)
>10	2092	580	1.36 (1.24–1.50)	1.32 (1.20–1.45)

aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

analysis showed similar results in all subgroups of age at appendectomy.

Several limitations are highlighted. One previous study showed a false positive diagnosis in 10.0% of patients with appendicitis and a false negative diagnosis in 6.0%[32]; this could potentially affect the results if these observed errors are present in this cohort; however, these will likely be similar in cases and controls and might therefore be nondifferential regarding results. Recent studies have shown noncomplicated appendicitis to be able to resolve with antibiotic treatment,[33–35] potentially highlighting unnecessary surgery. However, this does not apply to complicated appendicitis in which surgery is still recommended.[28,31] The risk of MC following appendectomy remained elevated independent of severity of appendicitis, supporting the observed association between MC and appendectomy due to appendicitis, albeit the absolute differences in the proportion of patients with a history of antecedent appendectomy were small. Furthermore, impact of healthcare utilization might induce bias in the results. Previous studies have attempted to handle this by identifying controls based on history of colonoscopies and healthcare visits.[36,37] Therefor, 2 post hoc sensitivity analyses were conducted. In the first analysis, controls with a previous colonoscopy were included, this reduced the number of eligible controls to 2588. Compared with the colonoscopy controls, no increased risk of MC was observed following appendectomy. In the second analysis, a proxy for healthcare utilization was included by adjusting for number of hospital visits. The risk of MC remained elevated, although the risk was slightly lower than in the main analysis. Data regarding primary care visits were not available when assessing healthcare utilization. When interpreting the results among patients with previous colonoscopy, we suggest caution due to the lower statistical power in the models, as well as due to the varying age pattern in this secondary model, and the fact that symptoms leading up to a colonoscopy may per se be linked to the exposure and outcome. However, the sensitivity analyses suggest that residual confounding may influence our results. Last, this study did not examine lifestyle factors because such data are not available. Smoking has been associated with both appendicitis and MC,[38–41] and obesity has shown an inverse association with MC.[42] In appendicitis, obesity has been associated with a higher risk of complicated disease.[43,44] Different lifestyle factors might thus have implications in the pathogenesis of both MC and appendicitis, possibly influencing the observed association.

Analysis on risk of future MC based on severity of appendicitis and follow-up time since appendectomy showed varying results. The highest risk was observed <1 year after noncomplicated appendicitis in cases overall, which might suggest misdiagnosis of MC inflammation in the appendix, rather than appendicitis, as the cause of appendectomy. Still, it should be noted that the number of cases in this group was low and the increased risk of MC was still observed after more than 10 years after appendectomy, contradicting the theory of misdiagnosis and strengthening the suggested association between appendectomy and MC. Further, complicated appendicitis could be argued less prone to detection bias. The highest associated risk for MC among patients with complicated appendicitis was observed 5–10 years after appendectomy, further suggesting a relation between appendectomy and MC. When stratifying the analyses on sex, the increased risk was observed both among men and women.

Table 3. Risk of Microscopic Colitis and per Subtype Following Appendectomy Compared With Controls, Stratified on Severity of Appendicitis

Years Since Appendectomy	Controls	Cases	OR (95% CI)	aOR (95% CI)
Microscopic colitis				
Complicated appendicitis				
<1 (subanalysis)	4	1	1.20 (0.13–10.72)	1.12 (0.13–10.04)
≥1 (overall)	632	172	1.34 (1.13–1.59)	1.29 (1.09–1.53)
1–<5	21	8	1.87 (0.83–4.23)	1.88 (0.83–4.27)
5–10	31	15	2.38 (1.28–4.41)	2.37 (1.28–4.40)
>10	580	149	1.26 (1.05–1.51)	1.21 (1.01–1.44)
Noncomplicated appendicitis				
<1 (subanalysis)	46	33	3.44 (2.20–5.38)	3.36 (2.14–5.26)
≥1 (overall)	1897	669	1.73 (1.58–1.90)	1.69 (1.55–1.85)
1–<5	163	66	1.99 (1.49–2.65)	2.00 (1.50–2.67)
5–10	180	84	2.29 (1.77–2.98)	2.28 (1.76–2.96)
>10	1554	519	1.64 (1.48–1.82)	1.60 (1.44–1.77)
Incidental appendectomy				
<1 (subanalysis)	0	0	N/A	N/A
≥1 (overall)	981	262	1.32 (1.14–1.51)	1.26 (1.10–1.45)
1–<5	2	0	N/A	N/A
5–10	18	12	3.28 (1.58–6.81)	3.27 (1.57–6.79)
>10	961	250	1.28 (1.11–1.47)	1.23 (1.07–1.41)
Collagenous colitis				
Complicated appendicitis				
<1 (subanalysis)	N/A	0	N/A	N/A
≥1 (overall)	211	70	1.63 (1.24–2.14)	1.56 (1.19–2.05)
1–<5	4	3	3.68 (0.82–16.45)	3.85 (0.85–17.46)
5–10	14	7	2.45 (0.99–6.08)	2.46 (0.99–6.13)
>10	193	60	1.53 (1.14–2.04)	1.45 (1.08–1.94)
Noncomplicated appendicitis				
<1 (subanalysis)	13	11	4.01 (1.80–8.96)	3.96 (1.77–8.88)
≥1 (overall)	533	211	1.94 (1.65–2.29)	1.90 (1.61–2.23)
1–<5	45	17	1.85 (1.06–3.24)	1.84 (1.05–3.23)
5–10	52	23	2.17 (1.33–3.55)	2.17 (1.33–3.56)
>10	436	171	1.92 (1.61–2.30)	1.87 (1.56–2.42)
Incidental appendectomy				
<1 (subanalysis)	N/A	0	N/A	N/A
≥1 (overall)	378	113	1.47 (1.19–1.81)	1.42 (1.15–1.76)
1–<5	N/A	0	N/A	N/A
5–10	4	6	7.36 (2.08–26.10)	6.99 (1.97–24.80)
>10	374	107	1.13 (1.37–1.75)	1.36 (1.09–1.69)
Lymphocytic colitis				
Complicated appendicitis				
<1 (subanalysis)	3	1	1.61 (0.17–15.45)	1.50 (0.16–14.47)
≥1 (overall)	421	102	1.19 (0.96–1.48)	1.15 (0.92–1.43)
1–<5	17	5	1.45 (0.53–3.93)	1.44 (0.53–3.91)
5–10	17	8	2.32 (1.00–5.37)	2.31 (0.99–5.37)
>10	387	89	1.13 (0.90–1.43)	1.09 (0.86–1.37)

Table 3. Continued

		Lymphocytic colitis		
		Complicated appendicitis		
Noncomplicated appendicitis				
<1 (subanalysis)	33	22	3.21 (1.87–5.51)	3.12 (1.82–5.36)
≥1 (overall)	1364	458	1.65 (1.48–1.84)	1.61 (1.45–1.80)
1–<5	118	49	2.04 (1.46–2.85)	2.06 (1.47–2.87)
5–10	128	61	2.35 (1.73–3.18)	2.32 (1.71–3.15)
>10	1118	348	1.53 (1.36 –1.73)	1.49 (1.32–1.68)
Incidental appendectomy				
<1 (subanalysis)	N/A	0	N/A	N/A
≥1 (overall)	603	149	1.22 (1.02–1.46)	1.17 (0.97–1.40)
1–<5	N/A	0	N/A	N/A
5–10	14	6	2.11 (0.81–5.49)	2.14 (0.82–5.58)
>10	587	143	1.20 (1.00–1.44)	1.15 (0.95–1.38)

aOR, adjusted odds ratio; CI, confidence interval; N/A, not applicable; OR, odds ratio.

The pathophysiology of MC is thought to be associated with a dysregulated immune response in the gut mucosa, in genetically predisposed individuals, and infiltration of T helper 17 (Th17) cell in the lamina propria of colon has been observed.[1] Similarly, appendicitis has been associated with upregulation of the Th17 pathway. A case-control study showed increased levels of proinflammatory markers downstream the Th17 pathway in serum from patients with complicated appendicitis but not patients with noncomplicated appendicitis or nonspecific abdominal pain.[45] Potentially, increased activation of the pathway in complicated appendicitis could play a role in the association between complicated appendicitis and MC. Differences in pathology in MC subtypes could explain the variances observed in the risks with severity of appendicitis and incidental appendectomy.

Previous studies examining the associated risk between appendectomy and MC showed no significant relation.[18,19] In one study, only 39 appendectomy cases were found in the MC group, with 28 found among controls.[18] The second study included 22 patients with a history of appendectomy among MC cases and 50 appendectomies among controls.[19] Subgroup analyses regarding severity of appendicitis or follow-up time were not conducted in either of these studies. The current study included 14,520 cases and assessed the associated risk across different time windows and severity of appendicitis, in line with previous studies investigating the relation between appendectomy and other IBD,[8,16] significantly expanding prior findings. Two post hoc sensitivity analyses were conducted, assessing the risk of MC among patients with a history of open umbilical hernia repair and knee arthroscopy. In the analysis assessing the risk of MC following open umbilical hernia repair, no increased risk was identified; however, in the sensitivity analysis following knee arthroscopy, an increased risk of MC was seen. This might suggest residual confounding in the study despite the adjustments conducted.

In conclusion, this nationwide case-control study found an increased risk of MC following appendectomy. Time since appendectomy and severity of appendicitis seem to influence the associated risk. Future studies on the suggested relation between the Th17 pathway, appendicitis, and MC may reveal common pathophysiological mechanisms linking appendicitis to future risk of developing MC and strengthening the observed association between MC and appendicitis. Furthermore, studies investigating the association between lifestyle factors, MC, and appendicitis are needed. Although an increased risk of MC was observed after appendectomy, we acknowledge appendectomy not to be a major risk factor for future MC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.05.037.

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Conflicts of Interest

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Supplementary Table 1. Surgical Procedure Codes Representing Appendectomy

Surgical Procedure	OPKOD	NOMESCO
Appendectomy "en passant"	0058	—
Appendectomy	4510	JEA00
Appendectomy + drainage		
Including appendectomy + drainage		JEA10
Including incision + drainage	4511	JAA00
Including laparotomy + drainage	4500	JAK00
Including laparoscopic drainage	4501	JAK01
Laparoscopic appendectomy	4517	JEA01

NOMESCO, Nordic Medico-Statistical Committee; OPKOD, operationskod (classification of surgery).

Supplementary Table 2. ICD Codes Defining Diagnosis of IBD

	ICD-7	ICD-8	ICD-9	ICD-10
Swedish National Patient Register	1964–1968	1969–1986	1987–1996	1997–present
Ulcerative colitis (UC)	572.20; 572.21; 578.03	563.10; 569.02	556	K51
Crohn's disease (CD)	572.00; 572.09	563.00	555	K50
IBD unclassified (IBD-U)	UC+CD or 572.30	UC+CD or 563.98; 563.99	UC+CD or 558	UC + CD, or K52.3

IBD, inflammatory bowel disease; ICD-7, International Classification of Diseases–Seventh Revision; ICD-8, International Classification of Diseases–Eighth Revision; ICD-9, International Classification of Diseases–Ninth Revision; ICD-10, International Classification of Diseases–Tenth Revision.

Supplementary Table 3. Definitions of Complicated and Noncomplicated Appendicitis

	Four-Digit Surgical Code (1965–1996)	NOMESCO (1997–Present)	ICD-7 (1964–1968)	ICD-8 (1969–1986)	ICD-9 (1987–1996)	ICD-10 (1997–Present)
Complicated appendicits						
Gangrenous			550.03	540.91	—	—
Perforation/rupture			550.10	540.00	540A	K35.0; K35.2
Abscess			550.13	540.03	540B	K35.1
Diffuse peritonitis with (or without) perforation/rupture or with abscess			550.11	540.01	—	K35.3
Appendectomy + drainage						
Including appendectomy + drainage		JEA10				
Including incision + drainage	4511	JAA00				
Including laparotomy + drainage	4500	JAK00				
Including laparoscopic drainage	4501	JAK01				
Appendectomy	4510	JEA00				
Laparoscopic appendectomy	4517	JEA01				
Noncomplicated appendicitis						
Acute/without peritonitis			550.00	—	540X	—
With localized peritonitis without abscess, possible perforation, or rupture			550.12	540.02	—	—
Phlegmonous			550.02	540.90	—	—
Suspected/NUD//unspecified			550.01; 551.99	540.99; 541.99	541	K35.8; K37
Appendectomy	4510	JEA00				
Laparoscopic appendectomy	4517	JEA01				

ICD-7, International Classification of Diseases–Seventh Revision; ICD-8, International Classification of Diseases–Eighth Revision; ICD-9, International Classification of Diseases–Ninth Revision; ICD-10, International Classification of Diseases–Tenth Revision; NOMESCO, Nordic Medico-Statistical Committee; NUD, non ultra descriptus.