APPENDECTOMY AND PROTECTION AGAINST ULCERATIVE COLITIS

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ABSTRACT

Background A history of appendectomy is rare in patients with ulcerative colitis. This suggests a protective effect of appendectomy or that appendicitis and ulcerative colitis are alternative inflammatory responses. We sought to characterize this inverse relation further.

Methods We studied a cohort of 212,963 patients who underwent appendectomy before the age of 50 years between 1964 and 1993 and a cohort of matched controls who were identified from the Swedish Inpatient Register and the nationwide census. The cohort was followed until 1995 for any subsequent diagnosis of ulcerative colitis.

Results Patients who underwent appendectomy for appendicitis and mesenteric lymphadenitis had a low risk of ulcerative colitis (for patients with perforated appendicitis, the adjusted hazard ratio was 0.58 [95 percent confidence interval, 0.38 to 0.87]; for those with nonperforated appendicitis it was 0.76 [95 percent confidence interval, 0.65 to 0.90]; and for those with mesenteric lymphadenitis it was 0.57 [95 percent confidence interval, 0.36 to 0.89]). In contrast, patients who underwent appendectomy for nonspecific abdominal pain had the same risk of ulcerative colitis as the controls (adjusted hazard ratio, 1.06; 95 percent confidence interval, 0.74 to 1.52). For the patients who had appendicitis, an inverse relation with the risk of ulcerative colitis was found only for those who underwent surgery before the age of 20 years ($P<0.001$).

Conclusions Appendectomy for an inflammatory condition (appendicitis or lymphadenitis) but not for nonspecific abdominal pain is associated with a low risk of subsequent ulcerative colitis. This inverse relation is limited to patients who undergo surgery before the age of 20 years. (N Engl J Med 2001;344:808-14.)

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THE cause of ulcerative colitis is not known. Reports of a low rate of appendectomy among patients with ulcerative colitis have therefore gained widespread attention.[1-11] It has been proposed that the excision of the appendix may have an immune-modulating effect that protects against ulcerative colitis. This hypothesis has been supported by some studies in animals.[12,13] It has been suggested that appendectomy could be used as a treatment for ulcerative colitis or as a prophylactic measure in persons at increased risk for ulcerative colitis.[14] The decrease in the appendectomy rate in Britain and Sweden during the past 50 years, however, has not been associated with an increase in the incidence of ulcerative colitis.[15-18]

Another explanation is that appendicitis and ulcerative colitis are alternative inflammatory responses that are genetically or environmentally determined. That environmental factors may play a part is supported by a study that reported a lower incidence of appendectomy and a higher incidence of ulcerative colitis among Mormons in Britain and Ireland than in the general population, possibly because of differences in lifestyle.[19]

We sought to characterize further the relation between appendectomy and ulcerative colitis. We used data from a national data base in Sweden to examine the influence of the specific diagnosis and the age of the patient at the time of appendectomy on the relation between appendectomy and ulcerative colitis in a case–control study.

METHODS

Study Population and Design

Since 1964, the Swedish National Board of Health and Welfare has compiled data on hospital discharges in its Inpatient Register. Besides a national registration number (that uniquely identifies every resident of Sweden), each record contains medical data, including surgical procedures performed (coded according to the Swedish Classification of Operations and Major Procedures[20]) and diagnoses at discharge (coded from 1964 to 1968 according to the 7th revision of the *International Classification of Diseases* [ICD-7],[21] from 1969 to 1986 according to the 8th revision [ICD-8],[22] and from 1987 to 1993 according to the 9th revision [ICD-9][23]). In 1964 the register included only six counties, representing 20 percent of the Swedish population, but more counties were added successively. Since 1987 the register has included data from all Swedish hospitals. Since there is virtually no private hospital care in Sweden, our study was essentially population based.

The study protocol was approved by the Swedish Data Inspection Board, a Swedish federal agency that serves as an institutional review board for linkages of data bases. This process has been approved by the institutional review committees at the various hospitals in Sweden.

Patients Who Underwent Appendectomy

All patients in the Inpatient Register who had a discharge diagnosis indicating that an appendectomy (operation code 4510 or 4511) had been performed between 1964 and 1993 were identi-

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fied (Table 1). Only patients who were under the age of 50 years at the time of surgery were included. Patients were divided into groups according to their discharge diagnoses, which included perforated appendicitis, nonperforated appendicitis, nonspecific abdominal pain, mesenteric lymphadenitis, and other diagnoses. Other diagnoses included salpingitis, gastroenteritis, ovarian cysts, inflammatory bowel disease, diverticulitis, other diseases of the appendix, and cholecystitis.

Control Patients

For each eligible patient with a history of appendectomy, one control patient without a history of appendectomy was matched according to age, sex, and township of residence. To establish the place of residence for all patients at the time of the surgery, we used data from the nationwide 1970, 1980, and 1990 censuses, and we chose the place of residence as that occupied closest to the time of the appendectomy. Consequently, for the patients who underwent appendectomy in the first half of each decade, the matching control was chosen from the census that preceded the operation. Eighty controls who died during the interval between the census and the operation were excluded from the analyses (Table 1).

Follow-up

Patients who underwent appendectomy and controls were linked to the Inpatient Register for 1964 to 1995. Patients with a discharge diagnosis of ulcerative colitis or ulcerative proctitis (ICD-7 code 57220 or 57221, ICD-8 code 56310 or 56902, or ICD-9 code 556X) were identified. Some patients had received different discharge diagnoses of inflammatory bowel disease at different times. Reassignment of the diagnosis may occur as the disease progresses or if the histopathological diagnosis after surgery does not correspond to the diagnosis at the time of the first discharge. The most recent discharge diagnosis was considered the final diagnosis. The date of the first diagnosis of any inflammatory bowel disease was considered the time of the final diagnosis.

The follow-up for both groups of patients started one year after the date of the appendectomy and ended at the time of a discharge diagnosis of ulcerative colitis, on the date of death, or on December 31, 1995, whichever came first. Case patients and controls who had a diagnosis of ulcerative colitis before or within one year after appendectomy were considered to have preexisting cases and were excluded. Finally, each case patient or control whose matched counterpart had been excluded was also excluded; i.e., only complete pairs of case patients and matched controls were included in the analysis. Thus, the patients with a history of appendectomy who were matched to the 80 controls who died between the census and the time of the appendectomy were also excluded.

Statistical Analysis

The risk of ulcerative colitis after appendectomy was analyzed by calculation of the incidence-rate ratio (the ratio of the incidence rates of ulcerative colitis among the patients who underwent appendectomy to that among the controls). The incidence rate is the number of diagnosed cases of ulcerative colitis divided by the total number of person-years at risk during follow-up. The exact confidence intervals were calculated as described by Rothman.[24]

Multivariate analyses were performed with Cox proportional-hazards regression to adjust for any confounding effect of sex, age at the time of surgery, and year of surgery. The modification of the effect of appendectomy by age at the time of surgery was analyzed by the inclusion of terms for the interaction between diagnosis and age at the time of surgery in the models. To summarize the evolution over time of the risk of ulcerative colitis after appendectomy, we used Kaplan–Meier analysis to construct curves for the cumulative incidence of ulcerative colitis among the case patients and the controls, which were then compared with use of the log-rank test. Separate analyses were performed for the subgroups of case patients who underwent appendectomy for appendicitis before the age of 20 and at or after the age of 20, for mesenteric lymphadenitis, and for nonspecific abdominal pain and the corresponding controls. All tests of significance were two-sided. A P value of less than 0.05 was considered to indicate statistical significance.

TABLE 1. REASONS FOR THE EXCLUSION OF CASE PATIENTS AND CONTROLS.*

VARIABLE	CASE PATIENTS	CONTROLS
	no.	
All patients	213,729	213,729
Reason for exclusion		
Ulcerative colitis at or before the appendectomy	220	168
Ulcerative colitis within one year after the appendectomy	74	24
Death within one year after the appendectomy	168	47
Dead at the time of the case patient's appendectomy†	—	80
Less than one year of follow-up	286	187
Eligible patients	212,963	212,963

*Each patient who underwent appendectomy was matched to one control patient according to age at the time of appendectomy, sex, and township of residence. The matching was based on the census that was nearest in time to the operation; the patients who underwent surgery in the first half of each decade were matched according to their residence before the operation. Only complete pairs of case and control patients were eligible. Some patients had more than one reason for exclusion.

†The control patients had died before the matched case patients underwent surgery.

RESULTS

The characteristics of the patients in the case and control groups are presented in Table 2. After exclusions, there were 212,963 case patients and the same number of controls for analysis (Table 1). The follow-up encompassed more than 5 million person-years. During this period, 770 patients with a discharge diagnosis of ulcerative colitis were identified. One hundred three of these patients were later reclassified as having Crohn's disease. Twenty-eight patients with a first diagnosis of indeterminate colitis and 19 with a first diagnosis of Crohn's disease were reclassified as having ulcerative colitis. Thus, there were 714 patients with a final diagnosis of ulcerative colitis.

Incidence-Rate Ratio

Patients who had an appendectomy had a significantly lower incidence of ulcerative colitis during follow-up than the controls (incidence-rate ratio, 0.74; 95 percent confidence interval, 0.64 to 0.86) (Table 3). This relation was found after appendectomy for appendicitis (incidence-rate ratio, 0.73; 95 percent confidence interval, 0.62 to 0.87) and for mesenteric lymphadenitis (incidence-rate ratio, 0.48; 95 percent confidence interval, 0.27 to 0.83). The relation was not found after appendectomy for nonspecific abdominal pain (incidence rate ratio, 1.34; 95 percent confidence interval, 0.77 to 2.38). The inverse relation of appendectomy to the risk of ulcerative colitis was ob-

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TABLE 2. CHARACTERISTICS OF THE COHORTS.*

CHARACTERISTIC	CASE PATIENTS (N=212,963)	CONTROLS (N=212,963)
Age at appendectomy (yr)	22.1±10.7	22.1±10.7
Duration of follow-up (yr)	13.3±7.3	13.3±7.3
Person-years of follow-up (no.)	2,829,628	2,835,038
Cases of ulcerative colitis (no.)	304	410
Age at diagnosis of ulcerative colitis (yr)	33.7±11.6	32.4±11.2

*Plus–minus values are means ±SD.

served only in patients who had undergone surgery before the age of 20 years.

Multivariate Analysis

The relation of ulcerative colitis with the patient's diagnosis at the time of appendectomy, with adjustment for age, time period, and sex, was analyzed with use of Cox proportional-hazards regression. Significant inverse relations with ulcerative colitis were found for appendectomy for perforated appendicitis (adjusted hazard ratio, 0.58; 95 percent confidence interval, 0.38 to 0.87; P=0.01), for nonperforated appendicitis (adjusted hazard ratio, 0.76; 95 percent confidence interval, 0.65 to 0.90; P=0.001), and for mesenteric lymphadenitis (adjusted hazard ratio, 0.57; 95 percent confidence interval, 0.36 to 0.89; P=0.02). Appendectomy for nonspecific abdominal pain had no relation with ulcerative colitis (adjusted hazard ratio, 1.06; 95 percent confidence interval, 0.74 to 1.52; P=0.78). An age of less than 20 years at the time of surgery (adjusted hazard ratio, 0.65; 95 percent confidence interval, 0.56 to 0.76; P<0.001) and female sex (adjusted hazard ratio, 0.84; 95 percent confidence interval, 0.72 to 0.98; P=0.02) were significant covariates in the model.

Effect Modification by Age at the Time of Surgery

The inclusion of terms of interaction between diagnosis and age at the time of surgery produced significant results for the interaction of age and nonperforated appendicitis (P<0.001) but not for the interaction of age and perforated appendicitis (P=0.07), probably because of the smaller sample. The other interaction terms were not significant.

Separate multivariate analyses were performed for patients who had surgery before the age of 20 and those who had surgery at 20 or older to assess the relation between appendectomy and ulcerative colitis in the two age groups. Patients who underwent surgery for appendicitis before the age of 20 had a low risk

TABLE 3. THE INCIDENCE RATE OF ULCERATIVE COLITIS AMONG CASE PATIENTS AND CONTROLS.

VARIABLE	NO. OF PAIRS	PERSON-YEARS OF FOLLOW-UP*		NO. OF PATIENTS WITH ULCERATIVE COLITIS		INCIDENCE OF ULCERATIVE COLITIS PER 100,000 PERSON-YEARS		INCIDENCE-RATE RATIO (95% CI)†
		CASE PATIENTS	CONTROLS	CASE PATIENTS	CONTROLS	CASE PATIENTS	CONTROLS	
All appendectomies	212,963	2,829,628	2,835,038	304	410	10.74	14.46	0.74 (0.64–0.86)
Appendicitis	163,954	2,154,914	2,157,183	234	320	10.86	14.83	0.73 (0.62–0.87)
Perforated	22,879	284,916	285,842	24	41	8.42	14.34	0.59 (0.34–0.99)
Nonperforated	141,075	1,869,998	1,871,341	210	279	11.23	14.91	0.75 (0.62–0.90)
Lymphadenitis	19,362	277,991	278,410	20	42	7.19	15.09	0.48 (0.27–0.83)
Nonspecific abdominal pain	16,322	211,392	212,856	32	24	15.14	11.28	1.34 (0.77–2.38)
Other diagnoses	13,325	185,331	186,589	18	24	9.71	12.86	0.76 (0.39–1.45)
Sex								
Male	107,072	1,422,054	1,426,205	171	221	12.02	15.50	0.78 (0.63–0.95)
Female	105,891	1,407,574	1,408,832	133	189	9.45	13.42	0.70 (0.56–0.88)
Age at appendectomy								
0–9 yr	18,531	258,041	258,242	14	27	5.43	10.46	0.52 (0.25–1.02)
10–19 yr	84,339	1,117,975	1,119,419	76	153	6.80	13.67	0.50 (0.37–0.66)
20–29 yr	58,642	792,965	794,548	115	124	14.50	15.61	0.93 (0.71–1.21)
30–39 yr	32,340	422,382	422,951	65	73	15.39	17.26	0.88 (0.63–1.26)
40–49 yr	19,111	239,265	239,878	34	33	14.27	13.76	1.04 (0.62–1.73)
Time of surgery								
1964–1969	13,190	374,205	375,594	33	54	8.82	14.38	0.61 (0.39–0.96)
1970–1979	62,580	1,243,935	1,246,731	132	193	10.61	15.48	0.69 (0.55–0.86)
1980–1989	98,344	1,054,469	1,055,670	120	154	11.38	14.59	0.78 (0.61–0.99)
1990–1993	38,849	157,019	157,043	19	9	12.10	5.73	2.11 (0.91–5.30)

*Because of rounding, not all categories sum to the totals shown.

†CI denotes confidence interval.

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of ulcerative colitis during follow-up, as compared with the controls (adjusted hazard ratio, 0.42; 95 percent confidence interval, 0.31 to 0.57; P<0.001). Patients who underwent surgery for appendicitis when they were 20 years of age or older had the same risk of ulcerative colitis as the controls (adjusted hazard ratio, 0.97; 95 percent confidence interval, 0.79 to 1.18; P=0.79).

Kaplan–Meier Analysis

Figures 1 and 2 show the cumulative proportion of patients in whom ulcerative colitis developed after appendectomy performed for appendicitis before the age of 20 and at or after the age of 20, after appendectomy for mesenteric lymphadenitis, and after appendectomy for nonspecific abdominal pain, as well as the cumulative proportion of matched controls with ulcerative colitis. The decreased risk after appendectomy for appendicitis before the age of 20 (P<0.001) and after appendectomy for mesenteric lymphadenitis (P=0.005) persisted for up to 30 years. There was no significant difference between the controls and the patients who had surgery for appendicitis at the age of 20 or older (P=0.68) or the patients who had surgery for nonspecific abdominal pain (P=0.27).

DISCUSSION

Our findings confirm the previously reported inverse relation between appendectomy and ulcerative colitis. The incidence of ulcerative colitis was low after appendectomy for inflammatory conditions such as appendicitis and lymphadenitis, but no relation was found after appendectomy for nonspecific abdominal pain. These findings suggest that the inflammatory condition preceding the appendectomy, rather than the appendectomy itself, is inversely related to the subsequent development of ulcerative colitis.

The inverse relation suggests that appendicitis and mesenteric lymphadenitis are related to different pathogenic factors from those related to ulcerative colitis. One such factor is known for Crohn's disease. Crohn's disease is mediated by type 1 helper T cells, whereas ulcerative colitis is mediated by type 2 helper T cells. A weak positive relation has been reported between appendectomy and Crohn's disease.[3,6-8] This may suggest that appendicitis is mediated by type 1 helper T cells, which would explain the inverse relation to ulcerative colitis. The pathogenesis of appendicitis, however, is not known.

Our findings also confirm a previous report of an influence of age at the time of surgery on the inverse relation.[6] This influence was found only after surgery for appendicitis, with an inverse relation to ulcerative colitis after surgery for appendicitis in childhood and adolescence and no relation after surgery for appendicitis in adulthood. This finding suggests an age-dependent difference in the pathogenesis of appendicitis. Such a difference would be consistent with the strong age-dependent variation in the incidence of appendicitis, which peaks during adolescence.[17]

The chief strengths of our study are its size and its design as a cohort study. Most previous studies analyzed the frequency of appendectomy in patients with preexisting and newly diagnosed cases of ulcerative colitis as compared with the frequency in matched control patients at orthopedic or dermatology outpatient clinics. Thus, there was a risk of selection bias and recall bias. This problem is also suggested by the unusually high proportion of controls who had undergone appendectomy, which reached 17 to 25 percent in some of these studies,[5,6,8] as compared with an estimated lifetime risk of 7 percent.[25]

Our study also has potential weaknesses. The specificity of a diagnosis of appendicitis is somewhat less secure than that of a diagnosis of a noninflamed appendix, since in the former case the surgeon may overdiagnose macroscopic pathologic changes. In a study of the Inpatient Register of Jönköping county in central Sweden, a region that is also included in the national register, 10 percent of patients had been given a false positive diagnosis of appendicitis and 6 percent had been given a false negative diagnosis.[17] These figures are probably representative of the whole register. The differentiation between mesenteric lymphadenitis and nonspecific abdominal pain is also imprecise. These errors, however, would only lead us to underestimate the differences we observed.

Epidemiologic studies have shown that appendicitis that resolves spontaneously is common.[17] A diagnosis of appendicitis may therefore be related to care-seeking behavior and other underlying socioeconomic factors. This potential source of selection bias, however, does not apply to patients with perforated appendicitis.

The specificity of the diagnoses of ulcerative colitis in the Swedish Inpatient Register was assessed in one previous study and was found to be about 90 percent.[18] We did not include patients with distal colitis or mild inflammation that did not necessitate hospital care. The inverse relation therefore applies only to patients with extensive colitis or severe inflammation. There is, however, no reason to believe that the underreporting of patients with mild ulcerative colitis should be different for the case patients and the controls. Among the controls, there was a cumulative incidence of 150 newly diagnosed cases of ulcerative colitis per 100,000 persons during follow-up. After we included the preexisting cases, the cumulative incidence was just under 300 per 100,000 persons. This is very close to the prevalence found in epidemiologic studies in Sweden during this period.[26] Thus, most cases of ulcerative colitis were probably identified.

Recent studies have reported an increased risk of appendectomy among the children of parents who smoke.[27,28] Smoking may therefore act as a confounder. Unfortunately, information about smoking was not available to us. In previous studies, the inverse relation

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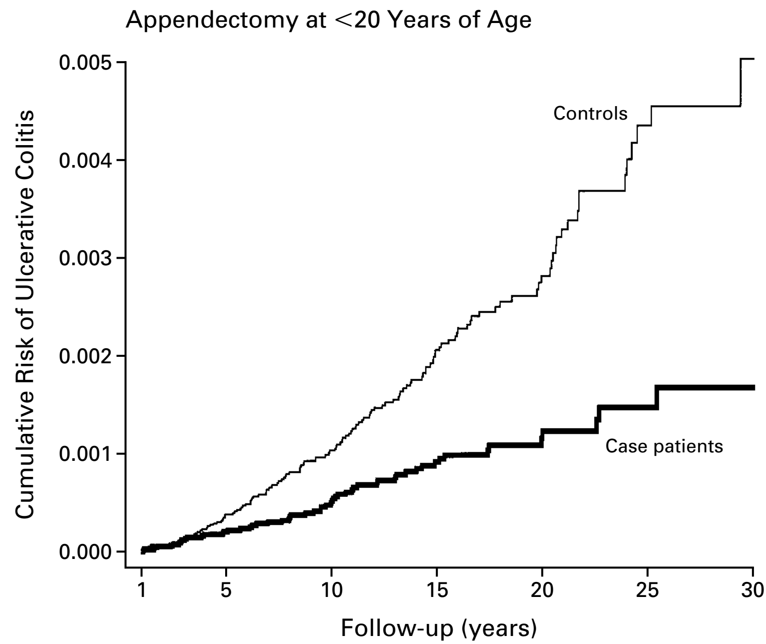
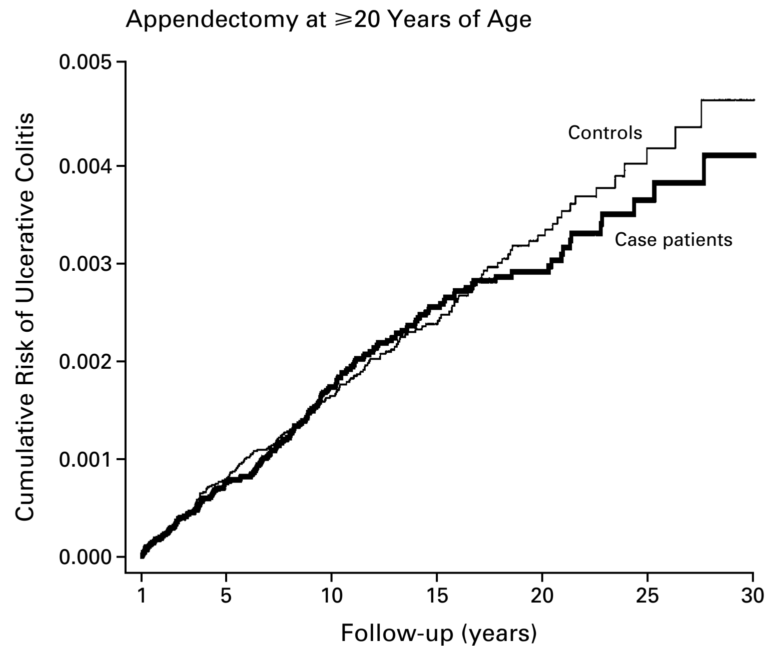


No. at Risk

Case patients	76,807	66,478	46,844	28,877	14,035	5249	1538
Controls	76,807	66,515	46,897	28,903	14,052	5263	1549



No. at Risk

Case patients	87,147	73,814	51,649	33,527	17,824	6070	1645
Controls	87,147	73,906	51,721	33,572	17,864	6123	1635

Figure 1. Kaplan–Meier Plots Showing the Cumulative Risk of Ulcerative Colitis after Appendectomy for Appendicitis before the Age of 20 Years ($P<0.001$) and at or after the Age of 20 Years ($P=0.68$), as Compared with the Risk in Matched Controls.

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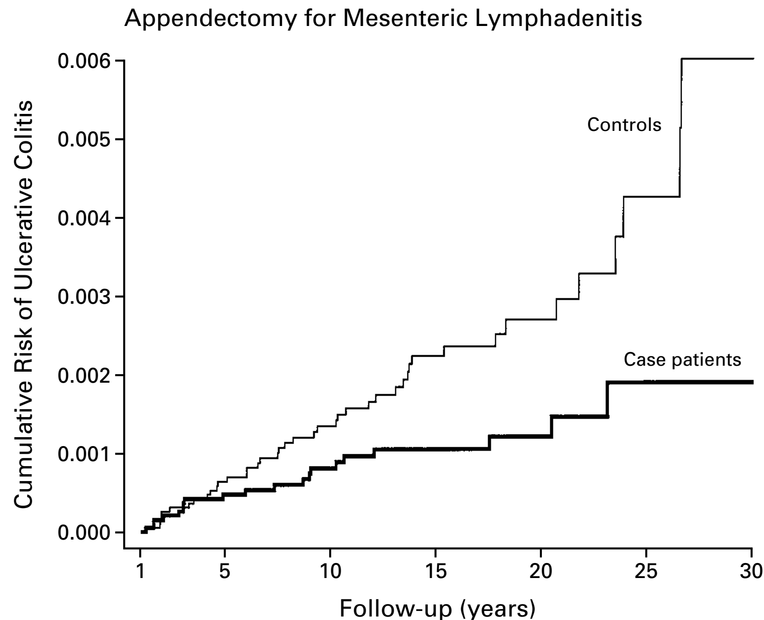
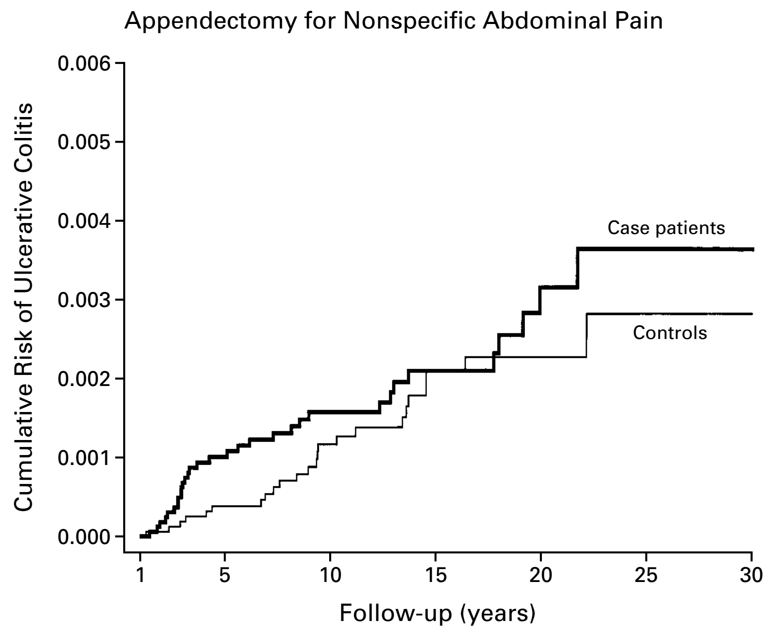


No. at Risk							
Case patients	19,362	17,381	13,361	8688	4279	1565	535
Controls	19,362	17,383	13,378	8720	4314	1567	538



No. at Risk							
Case patients	16,322	14,130	9879	6237	3047	534	83
Controls	16,322	14,188	9959	6314	3102	551	83

Figure 2. Kaplan–Meier Plots Showing the Inverse Relation between the Cumulative Risk of Ulcerative Colitis and Appendectomy for Mesenteric Lymphadenitis (P=0.005) and the Absence of Such a Relation after Appendectomy for Nonspecific Abdominal Pain (P=0.27), as Compared with the Risk in Matched Controls.

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between appendectomy and ulcerative colitis remained after adjustment for smoking status.[3,9,10]

In conclusion, we confirmed an inverse relation between appendectomy and ulcerative colitis. We found that this inverse relation was confined to appendectomy in young patients with inflammation in the appendix or mesenteric lymph nodes. We found no such relation for patients who had an appendectomy for nonspecific abdominal pain or for older patients who had surgery for appendicitis.

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CORRECTION

Appendectomy and Protection against Ulcerative Colitis

To the Editor: Like prior case–control studies, a follow-up study from Sweden (March 15 issue)[1] reported that appendectomy is associated with a low risk of subsequent ulcerative colitis. These findings have led to speculation about causality, suggestions that appendectomy might be therapeutic, and even proposals that appendectomy be performed prophylactically in first-degree relatives of patients.[2] These are not trivial conclusions. However, the literature on this subject is fraught with methodologic problems,[3] some of which are also present in the study by Andersson et al.[1]

Andersson et al. excluded 294 patients with ulcerative colitis that occurred at or before or within one year after the appendectomy, as compared with 192 of the controls — a difference of 102. That there was an excess number of case patients with ulcerative colitis who were excluded most likely occurred because patients with ulcerative colitis, whether established or incipient, can have symptoms so suggestive of appendicitis that surgery is indicated. It is not surprising that when outcomes among subjects with the exposure variable under evaluation, in this case appendectomy, are excluded from the study, a protective effect for that exposure is found in the remaining subjects.

Notably, the excess of 102 almost exactly matches the difference in the number of cases of ulcerative colitis reported during follow-up (304 among the case patients and 410 among the controls; a difference of 106), leaving the total number of cases of ulcerative colitis virtually identical in the two groups (598 and 602, respectively). Hence, the finding by Andersson et al. of an inverse association of appendectomy with the risk of ulcerative colitis can be accounted for by their exclusion policies. In a cohort study that addressed the same issue, we found no association between ulcerative colitis and appendectomy in 154,434 Danish patients who had undergone appendectomy.[3] In our view, there is also no effect of appendectomy on the risk of ulcerative colitis in the data analyzed by Andersson et al.

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To the Editor: The study by Andersson et al. strengthens the evidence that appendectomy is associated with a low risk of subsequent ulcerative colitis. Some aspects of the study, however, deserve comment. First, the mean age at the diagnosis of ulcerative colitis seems older (33.7 years) than the one usually reported in Scandinavian countries. Indeed, the first peak in the incidence of ulcerative colitis occurs between the ages of 20 and 25 years in Western countries.[1] Another report stated that the median age at diagnosis is 12.2 years in Sweden.[2] Could the authors have missed a significant number of patients?

A second concern is the lack of data on smoking status. Along with appendectomy, smoking has been repeatedly reported to confer protection against ulcerative colitis.[3] Thus, it may be an important confounding factor. A significant association between acute appendicitis and smoking in adults and passive smoking in children has been reported.[4]

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To the Editor: Andersson and coworkers suggest that appendectomy protects against ulcerative colitis, but only if it is performed before the age of 20 years. The alternative hypothesis — namely, that ulcerative colitis protects against appendicitis — is also attractive. Ulcerative colitis involves the mucosal lining of the bowel, and appendiceal lesions are common, especially in patients with less extensive colonic

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disease.[1] Destruction of the mucosal lining of the appendix in patients with ulcerative colitis could cause fibrosis and obliteration of the appendix, reducing the risk of subsequent obstructive appendicitis. Pathological changes, including fibrosis, were found in more than half of appendixes in patients undergoing colectomy for ulcerative colitis.[2]

If ulcerative colitis protects against appendicitis by inducing fibrosis within the appendiceal lumen, it would explain why the apparent protection of appendectomy against ulcerative colitis in the study by Andersson et al. was limited to younger patients. In the general population, the frequency of appendiceal fibrosis increases with age and might be similar to that in patients with ulcerative colitis.

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The authors reply:

To the Editor: The hypothesis that ulcerative colitis protects against appendicitis, suggested by Lowenfels and Maisonneuve, has been proposed by others who did not consider the temporal relation between appendectomy and ulcerative colitis. This interpretation of our results is not valid, since we selected patients whose appendectomy preceded their diagnosis of ulcerative colitis. In fact, the larger number of case patients with a diagnosis of ulcerative colitis before or at the time of appendectomy than of controls suggests that ulcerative colitis is a risk factor for appendicitis and appendectomy. This is also consistent with the findings of appendiceal inflammation in patients who underwent colectomy for distal ulcerative colitis.[1]

In response to the comments of Frisch and Biggar, we think it is correct to exclude patients in whom the study outcome has occurred before or at the time of the exposure. Similarly, in order to exclude patients who had undiagnosed ulcerative colitis at the time of the appendectomy, we also chose to start the follow-up one year after the operation.

We have reviewed our results and found one error in Table 1. Thirty-nine of the 74 case patients who were identified as having received a diagnosis of ulcerative colitis within the first year after the appendectomy had actually already been given the diagnosis at the time of the operation. The correct number of exclusions because of a diagnosis of ulcerative colitis before or at the time of appendectomy is therefore 259 case patients (instead of 220) and 168 controls.

We recalculated our results, starting the follow-up immediately after the appendectomy and including the 35 case patients and 24 controls who had been given a diagnosis of ulcerative colitis within one year after the operation. We found little change. The incidence-rate ratio of ulcerative colitis among the patients who underwent appendectomy for appendicitis as compared with the controls was 0.77 (95 percent confidence interval, 0.65 to 0.90); after appendectomy for mesenteric lymphadenitis it was 0.56 (95 percent confidence interval, 0.32 to 0.94); and after appendectomy for nonspecific abdominal pain it was 1.34 (95 percent confidence interval, 0.79 to 2.30). For the patients who underwent surgery for appendicitis before the age of 20 years it was 0.45 (95 percent confidence interval, 0.33 to 0.61), and for patients who underwent surgery at or after the age of 20 years it was 1.00 (95 percent confidence interval, 0.81 to 1.22).

Frossard et al. comment on the age at diagnosis of ulcerative colitis, which is older in our study than in other studies of ulcerative colitis. Since we included only patients who had received a diagnosis of ulcerative colitis more than one year after the appendectomy, the mean age at the start of follow-up was 23.1 years. In addition, had information regarding whether or not the subjects smoked been available, we believe it would have marginally affected our results. This has been the result in previous studies in which an adjustment for smoking status was made.[2,3,4,5]

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