

# Appendectomy and subsequent risk of inflammatory bowel diseases

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**Background.** Case-control studies have reported an inverse relationship between appendectomy and the risk of ulcerative colitis, but the association has not been confirmed in prospective studies.

**Methods.** Using national hospital discharge registry data in Denmark, the authors followed up 154,434 patients who underwent appendectomy during the period 1977 to 1989 to investigate whether they had subsequent hospitalizations for ulcerative colitis and Crohn's disease. Ratios of observed-to-expected first hospitalizations for inflammatory bowel diseases served as measures of the relative risk (RR).

**Results.** Hospitalization for ulcerative colitis occurred in 84 patients who had appendectomies versus 97.0 expected (RR = 0.87; 95% CI, 0.69-1.07). RRs were not significantly reduced in subgroups defined by sex, age, time since appendectomy, calendar period, or cause of appendectomy. Hospitalization for Crohn's disease occurred in excess (RR = 2.88; 95% CI, 2.45-3.39;  $n = 150$ ), notably in the first year after appendectomy (RR = 10.83; 95% CI, 8.49-13.62;  $n = 73$ ); but after 5 years, the RR was not significantly elevated.

**Conclusions.** This large population-based cohort study failed to support a significant inverse association between appendectomy and ulcerative colitis risk in the first decade after the operation. The excess of Crohn's disease shortly after appendectomy most likely reflects differential diagnostic problems in patients newly presenting with abdominal pain. (Surgery 2001;130:36-43.)

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THE ETIOLOGIES of ulcerative colitis and Crohn's disease (regional enteritis) remain unclear. An inheritable component is likely, but clear genetic associations have not been identified.<sup>1,2</sup> The only established environmental risk modifier is smoking, which is considered protective against ulcerative colitis but a risk factor for Crohn's disease.<sup>3</sup> Recently, Rutgeerts et al<sup>4</sup> claimed that appendec-

tomy was strongly protective against ulcerative colitis, and concordant observations from other case-control studies, with odds ratios generally between 0.2 and 0.5,<sup>5-20</sup> support the existence of an inverse association between appendectomy and ulcerative colitis risk. In contrast, several studies have found a moderately increased risk of Crohn's disease after appendectomy, with odds ratios between 1.3 and 1.7.<sup>5,7,8,15,17,19,21</sup> The contrast has nourished the hypotheses that appendectomy protects against ulcerative colitis or that certain genetic or environmental factors that increase the risk of appendicitis decrease the risk of ulcerative colitis.

On these grounds, it was recently suggested that appendectomy should be considered a possible therapeutic maneuver for patients with refractory ulcerative colitis and possibly a prophylactic measure in first-degree relatives of patients with ulcerative colitis.<sup>22</sup> Because case-control studies are prone to methodologic biases, however convincing their results may appear, we evaluated this issue in a prospective study. Specifically, we examined the

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risk of ulcerative colitis and Crohn's disease in a population-based cohort of more than 150,000 patients who underwent appendectomies and who were followed up for as much as 13 years after appendectomy.

## **METHODS**

Since 1977, a nationwide registration system has recorded more than 99% of all hospitalizations in Denmark.<sup>23</sup> For each hospitalization, the register contains the 10-digit personal identifier (incorporating codes for sex and date of birth) unique to each citizen in Denmark, date of discharge, surgical procedures, and medical discharge diagnoses. Procedures are coded according to a national classification system,<sup>24</sup> and diagnoses are coded according to a Danish version of the International Classification of Diseases, eighth edition (ICD8).<sup>25</sup> Using these population-based data, we previously reported on the cancer risks among patients undergoing appendectomy for acute appendicitis<sup>26</sup> and among patients hospitalized from 1977 to 1989 for inflammatory bowel disease.<sup>27-29</sup> We used data from these previous studies to examine the relationship between appendectomy and inflammatory bowel disease.

A total of 156,912 patients underwent appendectomy (operation code 43000) in Danish hospitals from 1977 to 1989. In these subjects, all previous, concurrent, and subsequent diagnoses of ulcerative colitis (ICD8 code 563.19) and Crohn's disease (ICD8 code 563.01) were identified. Non-Danish citizens ( $n = 869$ , 0.6%) and patients with invalid personal identifiers ( $n = 366$ , 0.2%) were excluded. We also excluded patients who underwent appendectomies who had a diagnosis of either ulcerative colitis ( $n = 113$ , 0.07%) or Crohn's disease ( $n = 133$ , 0.08%) registered before or at the time of appendectomy and, to minimize diagnostic ambiguity, patients who underwent appendectomies and who were registered at any time with both inflammatory bowel diseases ( $n = 38$ , 0.02%). Finally, we excluded patients who died during the hospital stay when the appendectomy was done ( $n = 959$ , 0.6%). The remaining cohort consisted of 154,434 appendectomy patients. Reasons for appendectomy were classified in 3 groups: perforating appendicitis (ICD8 code 540.00); other appendiceal disease, including nonperforating appendicitis, mucocele, fecalith, fistula, and unspecified appendiceal disease (ICD8 codes 540.01-543.09); and incidental appendectomy (ie, those with no diagnosis of appendiceal disease).

To determine the appropriate person-years at risk, we linked all appendectomy patients with the

National Causes of Death Registry to obtain dates of death. Person-years were counted from the date of discharge after appendectomy until a first hospitalization with inflammatory bowel disease, death, or January 1, 1990, whichever came first. For the calculation of expected numbers of patients hospitalized with inflammatory bowel diseases, we generated national first hospitalization rates for ulcerative colitis and Crohn's disease for men and women in 5-year age groups for the calendar periods 1977 to 1980, 1981 to 1984, and 1985 to 1989. These rates, shown previously to be a good proxy for incidence rates,<sup>30</sup> were based on first registered hospitalizations for 6569 patients (3104 men, 3465 women) with ulcerative colitis and 2820 patients (1111 men, 1709 women) with Crohn's disease identified in the discharge register for the period 1977 to 1989. Patients recorded to have both ulcerative colitis and Crohn's disease ( $n = 509$ ) were not included. For each stratum of sex, age, and calendar period, the expected number of patients with a first hospitalization for either ulcerative colitis or Crohn's disease was calculated as the product of stratum-specific first hospitalization rates and person-years at risk. These stratum-specific contributions were then added to yield the overall number of expected patients. The ratio of observed-to-expected numbers of patients served as the measure of relative risk (RR), and 95% CIs were calculated under the Poisson assumption.<sup>31</sup>

We analyzed the risk of hospitalization with inflammatory bowel disease according to strata of sex, calendar year, and time since appendectomy. Age-stratified analyses were done to evaluate the hypothesis that appendectomy performed before the age of 20 years confers particular protection against ulcerative colitis.<sup>19</sup> Finally, analyses stratified according to the reason for appendectomy addressed the hypothesis that appendicitis rather than appendectomy is associated with a low risk of ulcerative colitis.<sup>9</sup>

## **RESULTS**

Our cohort of 154,434 appendectomy patients (40% men, 60% women) included 10% who had the operation because of perforating appendicitis and 49% who had other appendiceal disease (Table I). The remaining 41%, referred to as having incidental appendectomies, either had the appendix removed incidentally during other abdominal surgery or had appendectomies for presumed appendicitis that was not confirmed by surgical findings. Approximately equal numbers of men and women had appendectomy because of perforating appendicitis or other appendiceal dis-

**Table I.** Characteristics of 154,434 patients followed up for inflammatory bowel disease after appendectomy in Danish hospitals, 1977-1989

	Men		Women		Total		Person-years*	Average follow-up (y)
	No.	%	No.	%	No.	%		
Year of appendectomy								
1977-1980	19,903	32%	31,173	34%	51,076	33%	536,795	10.5
1981-1984	19,568	31%	29,331	32%	48,899	32%	329,935	6.7
1985-1989	22,940	37%	31,519	34%	54,459	35%	138,197	2.5
Age at appendectomy								
< 20 y	29,497	47%	31,811	35%	61,308	40%	410,525	6.7
20-39 y	18,579	30%	29,820	32%	48,399	31%	330,585	6.8
40-59 y	7802	13%	19,274	21%	27,076	18%	176,490	6.5
60+ y	6533	10%	11,118	12%	17,651	11%	87,328	4.9
Cause of appendectomy†								
Perforating appendicitis	8407	13%	7199	8%	15,606	10%	94,192	6.0
Other appendiceal disease	39,689	64%	35,677	39%	75,366	49%	492,296	6.5
Incidental appendectomy	14,315	23%	49,147	53%	63,462	41%	418,439	6.6
Total	62,411	100%	92,023	100%	154,434	100%	1,004,928	6.5

\*Numbers are rounded; person-years do not add up to 1,004,928 in all stratifications.

†Perforating appendicitis: Patients with operation code 43000 (appendectomy) and ICD8-code 540.00 (acute appendicitis with perforation). Other appendiceal disease: Patients with operation code 43000 and ICD8-codes 540.01-540.99 (nonperforating acute appendicitis); 541.99-542.09 (other and unspecified appendicitis); or 543.01-543.09 (other and unspecified appendiceal disease, including mucocele, fecalith, fistula and unspecified appendiceal disease). Incidental appendectomy: Patients with operation code 43000 but no ICD8-code indicative of appendiceal pathology.

ease, whereas 77% of incidental appendectomies were performed in women. The median age at appendectomy was 21 years among men and 28 years among women. The cohort accrued a total of 1,004,928 person-years of follow-up with an average of 6.4 years among men and 6.6 years among women.

**Ulcerative colitis.** Overall, observed and expected numbers of patients with ulcerative colitis were similar. A total of 84 patients were subsequently hospitalized with ulcerative colitis versus 97.0 expected (RR = 0.87; 95% CI, 0.69-1.07; Table II). RRs were close to unity in all subgroups of sex, calendar year, age, and cause of appendectomy. Specifically, risk was not significantly reduced among persons who had appendectomies before the age of 20 years (RR = 0.74; 95% CI, 0.47-1.11; n = 23) or among patients with perforating appendicitis (RR = 0.70; 95% CI, 0.26-1.53; n = 6). Moreover, a subdivision of the observation time in periods less than 1 year, 1 to 4 years, and 5 to 13 years after appendectomy revealed no unusual risk in any follow-up interval (Figure).

**Crohn's disease.** Hospitalization with Crohn's disease occurred after appendectomy in 150 patients versus 51.9 expected (RR = 2.88; 95% CI, 2.45-3.39). A particular excess was seen in the first year after appendectomy (RR = 10.83; 95% CI, 8.49-13.62; n = 73), especially after incidental appendectomy (RR = 14.30; 95% CI, 10.47-19.07;

n = 46). However, after 5 years, no significant excess of Crohn's disease remained (RR = 1.33; 95% CI, 0.89-1.90; n = 29; Figure). Furthermore, there was no excess of Crohn's disease in the subgroup of patients who had appendectomies because of perforating appendicitis (RR = 0.96; 95% CI, 0.26-2.45; n = 4; Table II).

## DISCUSSION

This cohort study fails to support the previously reported association between appendectomy and risk of ulcerative colitis. We had considerable power to detect as statistically significant risk reductions of between 36% and 98% as reported in previous studies.<sup>4-20</sup> Indeed, our overall estimate of the RR (RR = 0.87; 95% CI, 0.69-1.07) excludes a reduction in the risk of ulcerative colitis after appendectomy of more than 31% and, being close to unity, suggests that there is no reduction at all. Our study has several advantages over previous investigations. It is a population-based cohort study with more than a million person-years of follow-up after appendectomy. We studied all men and women in Denmark who had their appendix removed during a 13-year period, and we used data on subsequent hospitalizations with ulcerative colitis and Crohn's disease that are considered to be valid and virtually complete.<sup>32</sup> Our results are consistent with the observation that rates of ulcerative colitis have remained relatively stable<sup>33</sup> during a

**Table II.** Relative risks (RRs) and 95% CIs of ulcerative colitis and Crohn's disease among 154,434 patients undergoing appendectomy in Danish hospitals, 1977-1989

	Ulcerative colitis cases			Crohn's disease cases		
	No. observed	No. expected	RR (95% CI)	No. observed	No. expected	RR (95% CI)
Sex						
Men	33	34.8	0.95 (0.65-1.33)	60	15.4	3.89 (2.97-5.01)
Women	51	62.2	0.82 (0.61-1.08)	90	36.5	2.47 (1.98-3.03)
Year of appendectomy						
1977-1980	45	54.7	0.82 (0.60-1.10)	56	27.7	2.03 (1.53-2.63)
1981-1984	28	30.3	0.92 (0.61-1.33)	53	17.0	3.12 (2.33-4.08)
1985-1989	11	12.0	0.92 (0.46-1.64)	41	7.3	5.65 (4.05-7.66)
Age at appendectomy						
< 20 y	23	31.1	0.74 (0.47-1.11)	40	20.3	1.97 (1.41-2.69)
20-39 y	34	37.7	0.90 (0.63-1.26)	80	19.8	4.05 (3.21-5.03)
40-59 y	14	17.1	0.82 (0.45-1.37)	25	7.9	3.15 (2.04-4.65)
60+ y	13	11.1	1.17 (0.62-2.00)	5	3.9	1.27 (0.41-2.97)
Cause of appendectomy						
Perforating appendicitis	6	8.5	0.70 (0.26-1.53)	4	4.2	0.96 (0.26-2.45)
Other appendiceal disease	40	45.7	0.88 (0.63-1.19)	61	24.6	2.48 (1.90-3.19)
Incidental appendectomy	38	42.8	0.89 (0.63-1.22)	85	23.2	3.67 (2.93-4.54)
Total	84	97.0	0.87 (0.69-1.07)	150	51.9	2.88 (2.45-3.39)

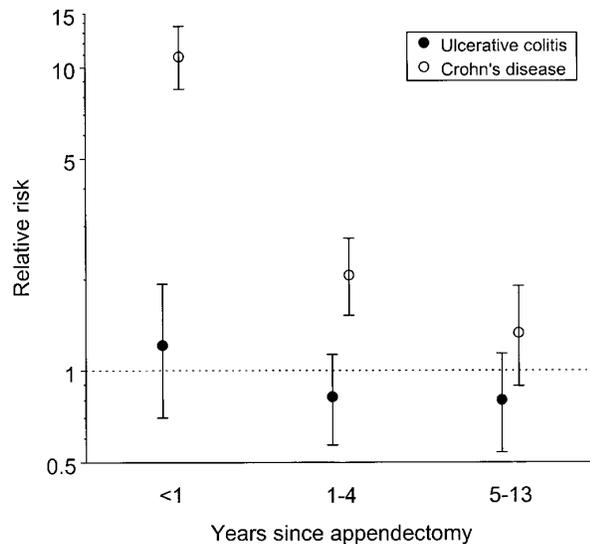
time when appendectomy rates have declined in several Western countries.<sup>34-38</sup>

Two hypotheses have been advanced to explain the observation in case-control studies of an inverse association between appendectomy and ulcerative colitis. One is that appendectomy per se may protect against ulcerative colitis. The underlying biologic speculation is that the appendix, a lymphoid organ with poorly understood immunologic properties, may somehow cause immunologic imbalance elsewhere in the mucosa of the large intestine, and that this imbalance may ultimately lead to ulcerative colitis.<sup>4</sup> As a consequence, removal of the appendix would be protective. It has been suggested, on the basis of animal studies,<sup>39</sup> that appendectomy performed before the age of 20 years might be particularly protective.<sup>19</sup> Our overall negative finding and the lack of a significant protective effect among such young patients fail to support this hypothesis. The other hypothesis is that factors predisposing a person to appendicitis might carry protection against ulcerative colitis.<sup>9</sup> However, the lack of convincing genetic, microbial, dietary, or other explanatory candidates and our finding of no significant reduction in ulcerative colitis risk after appendicitis-associated appendectomy detract from the credibility of this hypothesis.

Because right lower quadrant pain seen in Crohn's disease may mimic appendicitis, the positive association observed between appendectomy and Crohn's disease<sup>5,7,8,15,17,19,21</sup> has been attrib-

uted to differential diagnostic difficulties. Our data support this impression. In the current study, appendectomy for appendicitis with documented perforation was not associated with any unusual risk of Crohn's disease. However, appendectomy performed when no appendiceal disease was present was associated with a 14-fold increased risk of being hospitalized with Crohn's disease within 1 year. It is noteworthy that this remarkable excess of Crohn's disease was only reflected in case-control studies as marginal and often insignificant elevations in the odds ratios. Our overall estimates of the RRs for Crohn's disease (RR = 2.88) and ulcerative colitis (RR = 0.87) suggest that RR estimates in previous studies (RR ~1.3-1.7 for Crohn's disease and RR ~0.2-0.5 for ulcerative colitis) are both considerably too low. The resulting modest elevation in the risk of Crohn's disease thus appears to have served as an inappropriate assurance that the equally underestimated RR for ulcerative colitis was a true phenomenon of biologic importance and specificity.

We reviewed previous case-control studies<sup>4-21</sup> to examine methodologic reasons that might account for the observation of an inverse relationship between appendectomy and ulcerative colitis. Most investigations, but not all,<sup>4,9,11,15</sup> appropriately disregarded appendectomies done after a diagnosis of ulcerative colitis. However, only a few studies applied a complementary restriction to the controls.<sup>7,16,17</sup> Thus, appendectomies in control subjects performed after the onset of ulcerative colitis



**Figure.** Relative risks of first hospitalization for ulcerative colitis and Crohn's disease up to 13 years after appendectomy. Bars represent 95% CI.

the cases have greatly contributed to making this procedure appear more common in persons without ulcerative colitis. In 10 studies that did not use individual matching,<sup>4,9-15,20,21</sup> the impact of this bias would depend on the duration of the prevalence period of ulcerative colitis among case patients and on differences in the age distributions between cases and controls. None of these studies used incident cases of ulcerative colitis, and the average prevalence period among case patients was 8 years or more in those studies providing this information.<sup>9,11,13,15</sup> Control subjects were significantly older than patients in other studies,<sup>4,12,14</sup> and adjusting for age in the statistical analysis would not correct the over-ascertainment of irrelevant appendectomies among controls.

In addition to using unmatched or frequency matched case-control designs in studies with prevalent cases of ulcerative colitis, there were other common problems. Some studies used different methods for ascertaining the history of appendectomy in cases and controls.<sup>12,13</sup> A recent study<sup>18</sup> reported appendectomy frequencies were 3- to 5-fold higher when based on self-reports rather than on computerized medical records. This observation stresses the importance of using not only identical periods for ascertaining the appendectomy status, but also identical ascertainment methods in cases and controls. The extent to which this potentially important bias has hampered several other

studies that used more than one ascertainment method<sup>9,10,16,17,21</sup> is not known because the methods did not provide sufficient detail.

While no convincing genetic, microbial, or dietary hypothesis relates appendectomy to ulcerative colitis, smoking is believed to be protective against ulcerative colitis.<sup>3,40</sup> Smoking was recently reported to double the risk of appendectomy for acute appendicitis,<sup>41</sup> and, if so, it is a potential confounder in the association between appendectomy and ulcerative colitis. However, few studies took smoking into account.<sup>11,16,17</sup> The use of hospital controls in most previous studies\* might have created an inverse association with appendectomy because smokers are more likely to be hospitalized,<sup>42</sup> even among those admitted for injuries.<sup>43</sup>

Eight case-control studies selected control subjects on the basis of an individual matching procedure ensuring similar sex and age distributions among cases and controls.<sup>5-8,16-19</sup> Two of these<sup>8,19</sup> inappropriately disregarded the individual matching in the statistical analysis, and 3 studies<sup>5,6,18</sup> did not explicitly state whether they excluded appendectomies among controls that were performed after the onset of ulcerative colitis in the cases. The remaining 3 studies<sup>7,16,17</sup> reported significantly reduced odds ratios of 0.3 to 0.4. However, bias and confounding may also have been present in these studies as a result of lacking<sup>7</sup> or unspecified<sup>17</sup> control for differences in smoking habits, use of hospital controls,<sup>16</sup> possible differences in the ascertainment of appendectomies in cases and controls,<sup>16,17</sup> unspecified<sup>16</sup> or considerably lower<sup>17</sup> participation rates among controls than cases, and recall problems resulting from the use of prevalent cases.<sup>7, 17</sup> The importance of these limitations is uncertain. However, it is noteworthy that 1 of these studies<sup>17</sup> failed to observe a significant inverse relationship between appendectomy and ulcerative colitis risk when the analysis was restricted to incident cases.

We identified only a single case-control study<sup>21</sup> that did not support an inverse association between appendectomy and ulcerative colitis. Woods et al<sup>21</sup> reported that 15% of 65 patients with ulcerative colitis and 10% of 103 hypertension control subjects had a history of appendectomy (odds ratio = 1.7; 95% CI, 0.6-4.7). This study was reported only as a meeting abstract. It is possible that other studies failing to find significant associations were not reported because of difficulties associated with the publication of negative results.

Our study also has limitations. Because our registry data started in 1977, subjects could have been diagnosed with ulcerative colitis before that year. Because we were unable to identify and

\*References 4, 5, 9-12, 14-16, 19-21

exclude such prevalent patients, national hospitalization rates for ulcerative colitis used to calculate the expected number of ulcerative colitis cases for the appendectomy cohort were to some extent inflated by prevalent cases of ulcerative colitis. Persons with established ulcerative colitis are probably less likely to have an appendectomy than are healthy persons because nonspecific abdominal symptoms would be attributed to their disease rather than to possible appendicitis. Our finding of marginally lower than expected rates of ulcerative colitis in persons with appendectomies is likely to reflect this limitation in our study design and, consequently, the true RR of ulcerative colitis associated with appendectomy is likely to be even closer to unity than suggested by our data.

Like most previous studies, ours did not measure smoking at the individual level, but major confounding by smoking is unlikely in this study. We recently followed up those patients who underwent appendectomy because of appendicitis for the occurrence of cancer and observed 115 cases of lung cancer versus 114.4 expected cases (RR = 1.0).<sup>26</sup> However, lung cancer is not a sensitive measure of the smoker prevalence, and our appendectomy patients might be composed of more smokers than in the general population, as was observed in the United Kingdom.<sup>41</sup> If so, our RR estimate of 0.87 would be too low, and the true value closer to unity because smoking is believed to protect against ulcerative colitis.<sup>3,40</sup>

We may have missed a protective effect if long latency periods after appendectomy are required to induce protection. With a maximum of 13 years of follow-up, we had only limited data to examine the risk of inflammatory bowel disease beyond the first decade after appendectomy. Cohort studies in other settings and with longer periods of follow-up can overcome this limitation and examine whether appendectomy during childhood affects ulcerative colitis risk in adult life.

We studied only events of inflammatory bowel disease severe enough to require hospitalization, so our data cannot exclude a hypothetical inverse association restricted to milder cases of ulcerative colitis, such as those diagnosed and treated in office settings. Such a relationship, however, is hardly biologically plausible and would not account for the differences between findings in our prospective study and those of previous case-control studies. Most previous studies also recruited participants among hospitalized patients. Additionally, it has been suggested that appendectomy may be particularly protective against pancolitis,<sup>17</sup> a severe form

of ulcerative colitis that is highly unlikely to escape hospitalization.

## CONCLUSION

This study, the first based on prospective data from a large population-based cohort study, does not support a relationship between appendectomy and ulcerative colitis in the first decade after appendectomy. The association with Crohn's disease most likely reflects differential diagnostic problems in patients with abdominal pain. Additional cohort studies with longer follow-up are warranted, as are case-control studies of incident cases of ulcerative colitis and population controls using identical methods and periods for the ascertainment of previous appendectomies and potential confounders in the compared groups. Negative findings in this study, trends in rates of appendectomy and ulcerative colitis that do not support a protective effect, the lack of any convincing biologic rationale, and both established and possible methodologic problems in previous studies argue against a protective effect of appendectomy on future ulcerative colitis risk. The recent proposal to consider therapeutic appendectomy in patients with severe or refractory ulcerative colitis and prophylactic appendectomy among first-degree relatives of ulcerative colitis patients should not be implemented without credible evidence to support the hypothesis.

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## ADDENDUM

Since submission, 2 additional case-control studies and 1 follow-up study have been published.<sup>44-46</sup> Both case-control studies had methodological problems as seen in prior studies, including unmatched analysis of matched data,<sup>44</sup> use of different methods for ascertaining appendectomies in cases and controls,<sup>45</sup> and failure to specify the ascertainment period for appendectomies among controls.<sup>44,45</sup> A follow-up study in Sweden<sup>46</sup> compared incident hospitalization rates for ulcerative colitis for 212,963 subjects who underwent appendectomy and 212,963 individually matched comparison subjects. The authors reported a statistically significant overall risk reduction of 26% (RR = 0.74). However, the Swedish results are difficult to interpret.

During follow-up starting 1 year after appendectomy, Anderson et al<sup>46</sup> observed fewer hospi-

talizations (n = 304) for ulcerative colitis among appendectomized individuals than among the individually matched non-appendectomized group (n = 410). In contrast, appendectomized individuals had more ulcerative colitis diagnoses (n = 294) than non-appendectomized individuals (n = 192) in the period before the chosen starting point for follow-up. By study design, the comparison group was forced to remain non-appendectomized for the entire follow-up period. The excess diagnoses of ulcerative colitis before and up to 1 year after are likely to be the result of selection bias or surveillance bias or both. Selection bias may have occurred if eligible non-appendectomized comparison subjects were removed and transferred to the appendectomized group because of nonspecific abdominal pain in connection with incipient ulcerative colitis. A method to reduce the impact of such selection bias is to start follow-up after some reasonable latency period. The authors chose 1 year after appendectomy, which appears reasonable. However, the other component that may contribute to the excess of ulcerative colitis diagnoses in the appendectomy group before start of follow-up is surveillance bias. Appendectomies performed in the absence of appendicitis may have stimulated the search for the underlying reason for the patient's abdominal symptoms. When incipient ulcerative colitis was the explanation, the increased surveillance was likely to have resulted in the correct diagnosis rather shortly after removal of the non-inflamed appendix (and most likely within 1 year). The effect of such surveillance bias on the RR estimate can be minimized by shortening the latency period between appendectomy and start of follow-up. If, as in our analysis, Andersson et al<sup>46</sup> had started follow-up immediately after appendectomy, a change leading to inclusion of 74 and 24 early diagnoses of ulcerative colitis in appendectomized and non-appendectomized individuals, respectively (almost half of the reported 26% risk reduction associated with appendectomy), would be lost. Total numbers of diagnoses of ulcerative colitis would then amount to 378 and 438, respectively, for an overall RR of 0.86, which is remarkably close to our RR estimate of 0.87. The Swedish investigators had no means to disregard apparently incident ulcerative colitis diagnoses established before 1964, when their study began. Consequently, as in our study, the remaining marginal association in the Swedish study might be caused by differences between appendectomy rates among individuals with already established

ulcerative colitis and appendectomy rates in the general population.

#### REFERENCES

1. Orholm M, Munkholm P, Langholz E, Nielsen OH, Sørensen TIA, Binder V. Familial occurrence of inflammatory bowel disease. *N Engl J Med* 1991;324:84-8.
2. Podolsky DK. Inflammatory bowel disease. *N Engl J Med* 1991;325:928-37.
3. Thomas GA, Rhodes J, Green JT. Inflammatory bowel disease and smoking – a review. *Am J Gastroenterol* 1998;93:144-9.
4. Rutgeerts P, D'Haens G, Hiele M, Geboes K, Vantrappen G. Appendectomy protects against ulcerative colitis. *Gastroenterology* 1994;106:1251-3.
5. Gilat T, Hacoheh D, Lilos P, Langman MJ. Childhood factors in ulcerative colitis and Crohn's disease. An international cooperative study. *Scand J Gastroenterol* 1987;22:1009-24.
6. Higashi A, Watanabe Y, Ozasa K, Yan S, Hayashi K, Aoike A, et al. A case-control study of ulcerative colitis [Japanese]. *Nippon Eiseigaku Zasshi* 1991;45:1035-43.
7. Gent AE, Hellier MD, Grace RH, Swarbrick ET, Coggon D. Inflammatory bowel disease and domestic hygiene in infancy. *Lancet* 1994;343:766-7.
8. Wurzelmann JI, Lyles CM, Sandler RS. Childhood infections and the risk of inflammatory bowel disease. *Dig Dis Sci* 1994;39:555-60.
9. Smithson JE, Radford-Smith G, Jewell GP. Appendectomy and tonsillectomy in patients with inflammatory bowel disease. *J Clin Gastroenterol* 1995;21:283-6.
10. Marion JF, Bodian CA, Janowitz HD. Appendectomy, appendicitis, and inflammatory bowel disease [abstract]. *Gastroenterology* 1995;108:A870.
11. van Erpecum KJ, Smits SJ, van de Meeberg PC, Linn FH, Wolfhagen FH, vanBerge-Henegouwen GP, et al. Risk of primary sclerosing cholangitis is associated with nonsmoking behavior. *Gastroenterology* 1996;110:1503-6.
12. O'Gorman P, Bennett D, Kavanagh E, Twohig LB, O'Sullivan GC, O'Regan P, et al. MALTEctomy (appendectomy/tonsillectomy) does not influence the occurrence or mode of presentation of adult celiac disease. *Am J Gastroenterol* 1996;91:723-5.
13. Tasiopoulos J, Kavin H, Goldman J, Woseth D, Hanauer S. Appendectomy is protective against the development of ulcerative colitis [abstract]. *Gastroenterol* 1996;110:A1026.
14. Minocha A, Raczkowski CA. Role of appendectomy and tonsillectomy in pathogenesis of ulcerative colitis. *Dig Dis Sci* 1997;42:1567-9.
15. Breslin NP, McDonnell C, O'Morain C. Surgical and smoking history in inflammatory bowel disease: a case-control study. *Inflamm Bowel Dis* 1997;3:1-5.
16. Parrello T, Pavia M, Angelillo IF, Monteleone G, Riegler G, Papi G, et al. Appendectomy is an independent protective factor for ulcerative colitis: results of a multicentre case control study. *Ital J Gastroenterol Hepatol* 1997;29:208-13.
17. Russel MG, Dorant E, Brummer RJ, van de Kruijs MA, Muris JW, Bergers JM, et al. Appendectomy and the risk of developing ulcerative colitis or Crohn's disease: results of a large case-control study. *Gastroenterology* 1997;113:377-82.
18. Derby LE, Jick H. Appendectomy protects against ulcerative colitis. *Epidemiology* 1998;9:205-7.
19. Duggan AE, Usmani I, Neal KR, Logan RFA. Appendectomy, childhood hygiene, *Helicobacter pylori* status, and risk

- of inflammatory bowel disease: a case control study. *Gut* 1998;43:494-8.
20. Kubba AK, Price RF, Smith G, Palmer KR. Appendectomy and ulcerative colitis. *J R Coll Surg Edinb* 1998;43:244-5.
  21. Woods BL, Steinberg EN, Hornung CA, Vasudeva R, Howden CW. Does appendectomy really protect against ulcerative colitis? [abstract]. *Gastroenterology* 1995;108: A944.
  22. Schattner A. Appendectomy in ulcerative colitis [letter]. *Lancet* 1999;353:674.
  23. Danish National Board of Health. The activity in the hospital care system. Copenhagen, Danish National Board of Health, 1981.
  24. Danish National Board of Health. Classification of surgical procedures and therapies. Copenhagen, Danish National Board of Health, 1973.
  25. Danish National Board of Health. Classification of diseases. Copenhagen. Danish National Board of Health, 1976.
  26. Mellemkjær L, Johansen C, Linet MS, Gridley G, Olsen JH. Cancer risk following appendectomy for acute appendicitis (Denmark). *Cancer Causes Control* 1998;9:183-7.
  27. Mellemkjær L, Olsen JH, Frisch M, Johansen C, Gridley G, McLaughlin JK. Cancer in patients with ulcerative colitis. *Int J Cancer* 1995;60:330-3.
  28. Mellemkjær L, Johansen C, Gridley G, Linet MS, Kjaer SK, Olsen JH. Crohn's disease and cancer risk (Denmark). *Cancer Causes Control* 2000;11:145-50.
  29. Frisch M, Johansen C. Anal carcinoma in inflammatory bowel disease. *Br J Cancer* 2000;83:89-90.
  30. Fonager K, Sørensen HT, Olsen J. Change in incidence of Crohn's disease and ulcerative colitis in Denmark. A study based on the National Registry of Patients, 1981-1992. *Int J Epidemiol* 1997;26:1003-8.
  31. Breslow NE, Day NE. Statistical methods in cancer research. Vol. 2. The design and analysis of cohort studies. Lyon, France: International Agency for Research on Cancer, 1987:65-71. (IARC Scientific Publications no. 82.).
  32. Fonager K, Sørensen HT, Rasmussen SN, Møller-Petersen, Vyberg M. Assessment of the diagnoses of Crohn's disease and ulcerative colitis in a Danish hospital information system. *Scand J Gastroenterol* 1996;31:154-9.
  33. Russel MG, Stockbrugger RW. Epidemiology of inflammatory bowel disease: an update. *Scand J Gastroenterol* 1996;31:417-27.
  34. Noer T. Decreasing incidence of acute appendicitis. *Acta Chir Scand* 1975;141:431-2.
  35. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol* 1990;132:910-25.
  36. McCahy P. Continuing fall in the incidence of acute appendicitis. *Ann R Coll Surg Engl* 1994;76:282-3.
  37. Williams NM, Jackson D, Everson NW, Johnstone JM. Is the incidence of acute appendicitis really falling ? *Ann R Coll Surg Engl* 1998;80:122-4.
  38. Blomqvist P, Ljung H, Nyren O, Ekbohm A. Appendectomy in Sweden 1989-1993 assessed by the Inpatient Registry. *J Clin Epidemiol* 1998;51:859-65.
  39. Mizoguchi A, Mizoguchi E, Chiba C, Bhan AK. Role of appendix in the development of inflammatory bowel disease in TCR-alpha mutant mice. *J Exp Med* 1996;184:707-15.
  40. Jick H, Walker AM. Cigarette smoking and ulcerative colitis. *N Engl J Med* 1983;308:261-3.
  41. Montgomery SM, Pounder RE, Wakefield AJ. Smoking in adults and passive smoking in children are associated with acute appendicitis. *Lancet* 1999;353:79.
  42. Barendregt JJ, Bonneux L, van der Maas PJ. The health care costs of smoking. *N Engl J Med* 1997;337:1052-7.
  43. Sacks JJ, Nelson DE. Smoking and injuries: an overview. *Prev Med* 1994;23:515-20.
  44. Koutroubakis IE, Vlachonikolis IG, Kapsoritakis A, Spanoudakis S, Roussomoustakaki M, Mouzas IA, et al. Appendectomy, tonsillectomy, and risk of inflammatory bowel disease: case-controlled study in Crete. *Dis Colon Rectum* 1999;42:225-30.
  45. Dijkstra B, Bagshaw PF, Frizelle FA. Protective effect of appendectomy on the development of ulcerative colitis: matched, case-control study. *Dis Colon Rectum* 1999;42:334-6.
  46. Andersson RE, Olaison G, Tysk C, Ekbohm A. Appendectomy and protection against ulcerative colitis. *N Engl J Med* 2001;344:808-14.

### CORRECTION

The article "Consensus statement on submission and publication of manuscripts," which ran in the June issue of *Surgery* (2001;129:662-3), was incorrectly attributed to a single author. The article was written by the Surgical Journal Editors Group.