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The Association of Smoking and Surgery in Inflammatory Bowel Disease is Modified by Age at Diagnosis

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OBJECTIVES: We assessed the association of smoking at diagnosis of inflammatory bowel disease (IBD) on the need for an intestinal resection.

METHODS: The Health Improvement Network was used to identify an inception cohort of Crohn's disease ($n = 1519$) and ulcerative colitis ($n = 3600$) patients from 1999–2009. Poisson regression explored temporal trends for the proportion of newly diagnosed IBD patients who never smoked before their diagnosis and the risk of surgery within 3 years of diagnosis. Cox proportional hazard models assessed the association between smoking and surgery, and effect modification was explored for age at diagnosis.

RESULTS: The rate of never smokers increased by 3% per year for newly diagnosed Crohn's disease patients (incidence rate ratio (IRR) 1.03; 95% confidence interval (CI): 1.02–1.05), but not for ulcerative colitis. The rate of surgery decreased among Crohn's disease patients aged 17–40 years (IRR 0.96; 95% CI: 0.93–0.98), but not for ulcerative colitis. Smoking at diagnosis increased the risk of surgery for Crohn's disease patients diagnosed after the age of 40 (hazard ratio (HR) 2.99; 95% CI: 1.52–5.92), but not for those diagnosed before age 40. Ulcerative colitis patients diagnosed between the ages of 17 and 40 years and who quit smoking before their diagnosis were more likely to undergo a colectomy (ex-smoker vs. never smoker: HR 1.66; 95% CI: 1.04–2.66). The age-specific findings were consistent across sensitivity analyses for Crohn's disease, but not ulcerative colitis.

CONCLUSIONS: In this study, the association of smoking and surgical resection was dependent on the age at diagnosis of IBD.

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INTRODUCTION

Inflammatory bowel disease (IBD), consisting of Crohn's disease and ulcerative colitis, is a chronic, incurable condition of the gastrointestinal tract with increasing prevalence worldwide.[1] Most patients with IBD are prescribed medications to control disease activity,[2] and those who fail to respond to medical management often require an intestinal resection. Although the risk of surgery for Crohn's disease and ulcerative colitis has decreased over time, it remains relatively high.[3] The 10- year risk of intestinal resection is 47 and 16% for Crohn's disease and ulcerative colitis, respectively.[3]

The etiology of IBD is thought to arise from a combination of genetic and environmental risk factors, including smoking.[4,5] Smokers are less likely to develop ulcerative colitis compared to never smokers, but are at increased risk for developing Crohn's disease.[6] Smoking is also associated with a worse disease prognosis in Crohn's disease.[7] Studies have shown an association between smoking and an increased risk of surgery and postoperative recurrence.[8–13] In contrast, studies exploring the relationship between smoking and the prognosis of ulcerative colitis are inconsistent.[14–16]

As advances in medical management have likely accounted for the reduced risk of surgery in IBD,[11,12] studies have not adequately evaluated whether changes in smoking behavior have influenced the risk of surgery for IBD. A 2013 report from the United Kingdom (UK) National Statistics determined that the prevalence of cigarette smoking has decreased over the last three decades in the general population.[17] In 1980, 39% of UK adults smoked, whereas in 2010 this percentage decreased to 20%.[17] However, it is unclear whether the public health initiatives responsible for the decrease in smoking in the general population have also reduced the prevalence of smoking among newly diagnosed IBD patients and, in turn, reduced the risk of surgery for IBD.

Therefore, we conducted a study to explore changes in smoking and surgery risk in a nationally representative inception cohort of Crohn's disease and ulcerative colitis patients from the UK.

METHODS

Study design and patient data source. We performed a cohort study using The Health Improvement Network (THIN).

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THIN (version 2012–05) is an electronic database consisting of prospectively gathered medical records from over twelve million patients in the UK.[18] Patients registered in THIN are nationally representative and have a similar age, sex, and mortality distribution to that of the general UK population.[19,20] Approximately 6% of the UK population is registered in THIN. Vision software (London, UK), which provides a standardized system for data collection, was adopted by the over 560 THIN practices starting in the mid-1990s.[21] It is used to capture demographic data, medical diagnoses (in the form of Read codes), prescriptions, and laboratory data.[22]

Study population. External validation studies conducted on the General Practice Research Database—the precursor to the THIN database—have confirmed its reliability to identify cases of IBD.[23] Furthermore, studies of the General Practice Research Database and THIN have demonstrated that both databases have similar validity in data recording.[24] A validated list of Read codes was used to identify adults with Crohn's disease and ulcerative colitis (Appendix 1).[23] The inception cohort (newly diagnosed patients with IBD) were identified from 1999 until 2009; however, the study period spanned 1996–2012. We applied a 3-year backward washout period to differentiate incident from prevalent cases.[25] Newly diagnosed patients with IBD needed to be registered into the THIN database for at least 3 years before the first IBD code was identified. Further, incident cases of IBD were followed for at least 3 years following diagnosis.

Subjects were eligible for participation if they: (1) had at least 3 years of data in THIN before their Crohn's disease or ulcerative colitis diagnosis;[26,27] (2) had two or more codes for Crohn's disease or ulcerative colitis recorded, separated by a time interval of at least 4 weeks;[26] (3) did not have an intestinal surgery before their first IBD code in THIN; (4) were incident between 1999 and 2009 and following their practice's implementation of Vision software; and (5) had their smoking status recorded. Patients who were coded for both ulcerative colitis and Crohn's disease were excluded. The first IBD code that appeared in the database following the exclusion criteria was defined as the index date. Patients were followed from their first Crohn's disease or ulcerative colitis code until the earliest of migration out of practice, death, or last date of collection up to 2012. A flow diagram illustrating the selection of the study population is provided in Appendix 2.

Exposure and outcome identification. The primary outcome of interest was first intestinal resection for Crohn's disease or ulcerative colitis. Two experts independently searched Read codes to identify a list of intestinal surgeries (Appendix 3). Any disagreement in code identification was resolved by consulting a third party. The primary exposure of interest was cigarette smoking status at the diagnosis of Crohn's disease or ulcerative colitis. Previous studies of smoking in the General Practice Research Database have reported relatively high specificity and negative predictive values ($>90\%$) for identifying current, ex, and never smokers.[28] Smoking was defined as (1) never smoker, someone who was coded as a never smoker within 1 year (either before or after) of index or coded as a never smoker at the time of data collection; (2) ex-smoker, as someone coded for ex-smoking within 1 year of index; and (3) current smoker, as someone who was coded as a current smoker within 1 year of index. A subset of IBD patients were unclassifiable by smoking status at diagnosis because they were coded as either current or ex-smoker during the study period, but not within 1 year of index. The subset of patients whose smoking status could not be classified at diagnosis of IBD was excluded from our primary analysis. In a secondary analysis, we also explored the dose of smoking by stratifying current smokers into light smokers (defined as fewer than 10 cigarettes per day) and moderate to heavy smokers (defined as more than 10 cigarettes per day) at the index date.

Demographic information including age at index date, sex, and IBD medication use were additionally identified. Age at diagnosis was defined by the Montreal Classification:[29] (1) 17–40 years and (2) >40 years. Corticosteroid at diagnosis was explored as a marker for disease severity. Corticosteroid use at diagnosis was defined as prescription within 90 days of index because previous studies have identified corticosteroid use within 90 days as a risk factor for surgery.[30,31] Immunosuppressant use (azathioprine, 6-mercaptopurine, and methotrexate) was defined as immunosuppressant use for greater than 6 months before surgery.[32] In a secondary analysis, the role of C-reactive protein (CRP) was explored as a marker of disease activity.[33] CRP level was defined as the first CRP recording after index. CRP was explored as a dichotomous variable. Levels of <10 mg/l were defined as normal, and CRP 10 mg/l or greater were defined as elevated. The threshold value for CRP was *a priori* defined based on prior work from the THIN database.[34]

Data analysis. Characteristics of patients stratified by disease type (i.e., Crohn's disease vs. ulcerative colitis) and by age at diagnosis were explored descriptively. To test the hypothesis of temporal trends in the reduction of smoking, and that fewer newly diagnosed IBD patients would have a history of smoking before their diagnosis, we calculated the rate of newly diagnosed IBD patients who were classified as "never smoking" at their index date. We used a modified Poisson regression for binary outcomes to explore temporal trends from 1999 to 2009. Estimates were reported as incidence rate ratios (IRR) and accompanying 95% confidence interval (CI).

The 1, 3, and 5-year cumulative incidences of the first intestinal resection for Crohn's disease and ulcerative colitis following index were estimated using the Kaplan–Meier method. Poisson regression was used to assess whether the risk of surgery within 3 years of diagnosis decreased for cases incident between 1999 and 2009. For this analysis, patients with IBD were followed from 1999 to 2012 to allow for at least a 3-year follow-up period.

The association of smoking and the first intestinal resection was explored using survival analysis. The log-rank test was used to identify differences in time to first surgery among those who never smoked, quit smoking before diagnosis, and were actively smoking at diagnosis. For the log-rank test, the IBD patients who smoked but were unclassifiable as current or ex-smokers at index were excluded. Next, Cox proportional hazard models were used to assess the association between smoking and first surgery after adjusting for the following

a priori defined covariates:[31] age at index, sex, immunosuppressant use for at least 6 months, and steroid use within 90 days of index. Age was *a priori* explored as a potential effect modifier by analyzing its interaction with smoking status. When the *P* value associated with the interaction term was significant, the analysis was stratified by the effect modifier and two separate models were reported (one model for each level of the effect modifier). Estimates were reported as hazard ratios (HR) and accompanying 95% CIs. The Cox proportional hazards assumption was tested to ensure model assumptions were not violated.

Sensitivity analyses. Several sensitivity analyses were conducted. First, we restricted the study population to IBD patients with a CRP value. CRP (defined as above or below 10 mg/l) was included in the Cox proportional hazard model. Second, we analyzed the subset of our population who had their dose of smoking recorded in the database. A variable denoting light smokers (i.e., <10 cigarettes per day) vs. moderate-to-heavy smokers (i.e., ≥ 10 cigarettes per day) was included in the Cox proportional hazard model. Third, we included the patients with IBD who had a history of smoking, but were unclassifiable by smoking status (current vs. ex-smokers) within 1 year of the date of diagnosis. For these patients we used smoking status recorded throughout the study period (i.e., not restricted to within 1 year of the index date) to classify the patient as a current or ex-smoker at the index date. Fourth, in order to minimize misclassification of prevalent cases as incident, we performed sensitivity analyses to extend the backward washout period from 3 to 5 years.

All analyses were performed using Stata version 11.2 (StataCorp, College Station, TX) using a predetermined alpha of 0.05. The Conjoint Health Research Ethics Board at the University of Calgary approved the study protocol.

RESULTS

Crohn's disease. We identified 1,519 incident Crohn's disease cases diagnosed between 1999 and 2009. The patient characteristics are presented in Table 1. The rate of never smoking before Crohn's disease diagnosis increased by 3% per year (IRR: 1.03; 95% CI: 1.02–1.05) from 1999 to 2009 (Figure 1). The increase in never-smokers at diagnosis was observed for adults diagnosed between the ages of 17 and 40 years (IRR: 1.03; 95% CI: 1.01–1.05) and after 40 years (IRR: 1.04; 95% CI: 1.02–1.07).

The 1, 3, and 5-year cumulative incidences of first intestinal resection for Crohn's disease were 7.3% (95% CI: 6.1–8.7%), 12.4% (95% CI: 10.8–14.2%), and 15.8% (95% CI: 13.9–17.9%), respectively. The 1, 3, and 5-year risk of surgery for Crohn's disease stratified by age at diagnosis is provided in Appendix 4. Overall, the rate of surgery within 3 years of diagnosis was stable between 1999 and 2009 (IRR: 0.97; 95% CI: 0.93–1.02). When the time trend analysis was stratified by age at diagnosis, the 3-year rate of surgery decreased during the study period among patients with Crohn's disease diagnosed between the ages of 17 and 40 years (IRR: 0.96; 95% CI: 0.93–0.98), but not in those diagnosed after age 40 years (IRR: 1.01; 95% CI: 0.87–1.16).

In the multivariate analysis, effect modification was identified by age at diagnosis for smoking. In the younger age category (17–40 years), smoking status was not associated with first surgery for Crohn's disease after adjusting for covariates (Table 2). However, among patients diagnosed with Crohn's disease after the age of 40 years, smoking at diagnosis increased the risk of first surgery (HR: 2.99; 95% CI:

Table 1 Patient characteristics of Crohn's disease and ulcerative colitis patients

	Crohn's disease, *N* = 1519	Ulcerative colitis, *N* = 3600
Age, %		
17–40 years	66.4	46.4
>40 years	33.6	53.6
Sex, %		
Female	58.8	51.1
Male	41.2	48.9
Smoking, %		
Never-smoker	44.6	50.1
Ex-smoker	11.2	19.3
Current-smoker	18.7	8.6
Unclassifiable[a]	25.5	22.1
Medications, %		
Corticosteroid[b]	37.4	45.1
Immunomodulator[c]	31.7	18.4
C-reactive protein[d]		
<10 mg/l	63.4	77.8
≥10 mg/l	36.6	22.2
Disease duration[e]		
Median (Q1, Q3)	4.6 (2.7, 7.4)	5.4 (3.2, 7.9)

[a]Patients were smokers; however, we were unable to classify as current- or ex-smoker at diagnosis of Crohn's disease.
[b]Corticosteroid use within 90 days of index.
[c]Immunomodulator use for 6 months before surgery, but does not include anti-tumor necrosis factor therapies.
[d]C-reactive protein (CRP) was analyzed in a subset of Crohn's disease ($n = 1132$) and ulcerative colitis ($n = 2585$) patients with available data on CRP after the diagnosis of inflammatory bowel disease (IBD).
[e]Years from disease diagnosis until first surgery or study end.

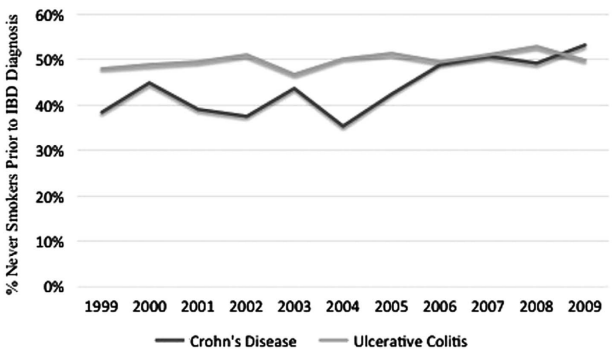

Figure 1 Proportion of patients without a prior history of smoking prior to the diagnosis of inflammatory bowel disease (IBD). The rate of never-smokers at diagnosis significantly increased over time for Crohn's disease (incidence rate ratio (IRR): 1.03; 95% CI: 1.02–1.05), but not for ulcerative colitis (IRR: 1.01; 95% confidence of interval (CI): 1.00–1.01).

Table 2 Adjusted hazard ratios (HR) for risk of first intestinal resection for Crohn's disease and ulcerative colitis, stratified by age at diagnosis

	Crohn's disease		Ulcerative colitis	
	Hazard ratio (95% CI), 17–40 years, *N* = 744	**Hazard ratio (95% CI), > 40 years, *N* = 372**	**Hazard ratio (95% CI), 17–40 years old, *N* = 1325**	**Hazard ratio (95% CI), > 40 years old, *N* = 1471**
Smoking				
Never-smoker[a]				
Ex-smoker	0.99 (0.57–1.72)	1.37 (0.57–3.29)	1.66 (1.04–2.66)	1.25 (0.77–2.04)
Current-smoker	0.85 (0.55–1.29)	2.99 (1.52–5.92)	0.37 (0.14–1.01)	1.64 (0.85–3.16)
Sex				
Female[a]				
Male	1.14 (0.80–1.62)	1.10 (0.59–2.06)	1.12 (0.76–1.64)	1.95 (1.21–3.15)
Corticosteroid[b]				
No[a]				
Yes	1.52 (1.07–2.15)	2.21 (1.18–4.12)	1.84 (1.25–2.73)	2.38 (1.48–3.81)
Immunosuppressant[c]				
No[a]				
Yes	0.52 (0.35–0.77)	0.58 (0.26–1.27)	0.63 (0.39–1.01)	1.46 (0.87–2.44)

CI, Confidence interval.
[a]Referent.
[b]Corticosteroid use within 90 days of index.
[c]Immunosuppressant use for at least 6 months before surgery.

Table 3 Sensitivity analyses for the association between current smoking and risk of first intestinal resection in Crohn's disease and the association between ex-smoking and risk of colectomy in ulcerative colitis

	Crohn's disease		Ulcerative colitis	
	Hazard ratio (95% CI), 17–40 years old, current- vs. never-smoker	**Hazard ratio (95% CI), > 40 years old, current- vs. never-smoker**	**Hazard ratio (95% CI), 17–40 years old, ex-smoker vs. never-smoker**	**Hazard ratio (95% CI), > 40 years old, ex-smoker vs. never-smoker**
Subset of patients with CRP[a]	0.93 (0.59–1.47)	2.65 (1.24–5.67)	1.51 (0.90–2.53)	1.09 (0.63–1.86)
Includes IBD patients who smoked, but were not classified as current or ex-smokers at the index date[b]	0.87 (0.62–1.23)	2.95 (1.56–5.58)	1.12 (0.75–1.67)	1.41 (0.94–2.14)
Backward washout period defined as 5 years[c]	0.85 (0.55–1.30)	3.16 (1.58–6.32)	1.58 (0.97–2.57)	1.20 (0.72–1.97)

CI, Confidence of interval; CRP, C-reactive protein; IBD, inflammatory bowel disease.
[a]Cox proportional hazard model is adjusted for CRP, sex, immunosuppressants, and corticosteroids.
[b]Cox proportional hazard model is adjusted for sex, immunosuppressants, and corticosteroids.
[c]Minimum registry in THIN for 5 years before index.

1.52–5.92) when compared to never-smokers after adjusting for covariates (Table 2).

Among current-smokers, we stratified Crohn's disease patients into light smokers and moderate-to-heavy smokers. Effect modification by age was not observed and the risk of surgery did not differ between moderate-to-heavy smokers and light smokers (HR = 1.02; 95% CI: 0.54–1.93). In the subset of patients with CRP recorded, smoking remained a significant risk factor for surgery (HR: 2.65; 95% CI: 1.24–5.67) after adjusting for an elevated CRP among those diagnosed after the age of 40 years (Table 3). After including the unclassifiable smoking patients, current-smoking status remained a significant risk factor for surgery (HR: 2.95; 95% CI: 1.56–5.58) for those diagnosed with Crohn's disease after the age 40 (Table 3). Restricting the analysis to a 5-year washout period excluded 74 people. Current-smoking status again remained a significant risk factor for surgery in the older age category (HR: 3.16; 95% CI: 1.58–6.32) when using the 5-year washout period (Table 3).

Ulcerative colitis. We identified 3,600 ulcerative colitis patients who were newly diagnosed between 1999 and 2009. The patient characteristics are presented in Table 1. The rate of never-smoking status before ulcerative colitis diagnosis was stable (IRR: 1.01; 95% CI: 1.00–1.01) from 1999 to 2009 (Figure 1). The temporal trend analysis did not differ for patients diagnosed with ulcerative colitis between the ages of 17 and 40 years (IRR: 1.00; 95% CI: 0.99–1.01)

and for those diagnosed over the age of 40 years (IRR: 1.01; 95% CI: 1.00–1.02).

The 1, 3, and 5-year cumulative incidences of colectomy for ulcerative colitis were 2.1% (95% CI: 1.7–2.7%), 4.8% (95% CI: 4.1–5.6%), and 6.7% (95% CI: 5.9–7.7%), respectively. The 1, 3, and 5-year risk of surgery for ulcerative colitis stratified by age at diagnosis is provided in Appendix 4. The rate of colectomy within 3 years of diagnosis did not change between 1999 and 2009 (IRR: 0.99; 95% CI: 0.95–1.03). When the time trend analysis was stratified by age at diagnosis, the 3-year risk of surgery did not change for patients with ulcerative colitis diagnosed between the ages of 17 and 40 years (IRR: 1.01; 95% CI: 0.96–1.07) or after 40 years (IRR: 0.95; 95% CI: 0.89–1.02).

Effect modification by age was identified for smoking. In the older age category ($>$40 years), smoking status was not associated with colectomy after adjusting for covariates (Table 2). In contrast, patients with ulcerative colitis diagnosed between the ages of 17 and 40 years and who quit smoking before the diagnosis of ulcerative colitis were significantly more likely to undergo a colectomy (ex-smoker vs. never-smoker: HR: 1.66; 95% CI: 1.04–2.66) within 3 years of their diagnosis (Table 2). However, the association between ex-smoking and colectomy was not significant in sensitivity analyses that evaluated patients with CRP data available (ex-smoker vs. never smoker: HR: 1.51; 95% CI: 0.90–2.53), and that included smokers whose quitting status was unclassifiable at the index date (ex-smoker vs. never-smoker: HR: 1.12; 95% CI: 0.75–1.67) (Table 3). Restricting the analysis to a 5-year washout period excluded 135 people. The magnitude of the association between ex-smoking and colectomy was similar to the primary analysis, though no longer statistically significant (HR: 1.58; 95% CI: 0.97–2.57) (Table 3).

DISCUSSION

This study suggests that the association of smoking and the need for an intestinal resection for patients with IBD is dependent on the age at diagnosis. From 1999 to 2009, patients diagnosed with Crohn's disease between the ages of 17 and 40 years were less likely to smoke over time, had a reduced risk of surgery within 3 years of diagnosis, and lacked a significant association between smoking status at diagnosis and their first intestinal resection. However, patients over the age of 40 years at time of Crohn's disease diagnosis who smoked were three times more likely to require surgery as compared to never smokers. The age-specific associations for Crohn's disease were consistent across sensitivity analyses. In contrast, smoking cessation before diagnosis of ulcerative colitis was associated with an increased risk of colectomy among those diagnosed between the ages of 17 and 40 years. Associations for ulcerative colitis were not statistically significant in sensitivity analyses.

Some, but not all, prior studies have shown that smoking increases the risk of surgery for Crohn's disease.[9,11,14,15,35–37] Not stratifying the risk of surgery by age at diagnosis may explain the heterogeneity in results among previous studies. In our study, smoking only increased the risk of surgery among Crohn's disease patients diagnosed after the age of 40 years. Other age-specific environmental risk factors have been previously reported. For example, air pollution was shown to increase the risk of developing early-onset Crohn's disease; however, this association was not observed in older adults newly diagnosed with Crohn's disease.[27] Thus, this study highlights the importance of stratifying IBD patients by age at diagnosis when evaluating the effects of environmental risk factors.

Our data suggest that the effect of smoking on the need for surgery in Crohn's disease requires several decades of exposure. Those diagnosed after age 40 almost certainly have a greater pack-year history of smoking. Prior data suggest that smoking contributes to stricture and fistula formation,[38] which could imply that smokers who were diagnosed with Crohn's disease after age 40 had a longer period between the onset of disease and diagnosis.[39] Public health initiatives implemented over the past several decades have discouraged smoking in the general population.[40] These programs target young people and may have contributed to a lower incidence of smoking. This theory is consistent with our finding that the proportion of never-smokers at diagnosis of Crohn's disease has increased across time.

The paradoxical relationship of smoking status in Crohn's disease and ulcerative colitis is well documented in the literature.[6] We observed that ulcerative colitis patients who were diagnosed between the age of 17 and 40 years and who quit smoking before the diagnosis of ulcerative colitis were more likely to require colectomy. However, the age-specific differential effect of smoking cessation on the risk of colectomy was not confirmed in sensitivity analyses that controlled for CRP and assessed our methodological assumptions. Further, prior studies have inconsistently shown that current-smokers with ulcerative colitis were less likely to require a colectomy and those who quit smoking were at increased risk of colectomy.[14–16]

The biological mechanism by which smoking may influence IBD is not known; however, several theories have been proposed. Smoking may selectively modulate the T-helper cell 1 (Th1) pathway that drive inflammation in Crohn's disease.[4] Smoking has also been shown to have separate effects on dendritic cells between Crohn's disease and ulcerative colitis patients.[41] Smoking may also influence colonic mucus formation and lead to endothelial dysfunction.[42,43] Smoking also alters the intestinal microbiome, which may influence the prognosis of IBD.[44] However, future studies are necessary to comprehensively explain the mechanism that explains the age-specific effects of smoking on the risk of surgery in IBD.

This paper has several strengths including large sample size allowing for powered analyses for effect modification, comprehensive data on smoking that is often missing from administrative databases, and selecting population-based cases that are representative of the general population. In addition, we accounted for disease duration (i.e., time from diagnosis to surgery) by analyzing our data using survival analysis. Further, the cumulative incidences of surgery were consistent with those reported in the literature. The estimates from our cohort, which began in 1999, are consistent with surgery estimates reported in cohorts of incident cases identified after the year 2000.[3]

Despite these strengths, several limitations should be considered.[45] We *a priori* stratified age at diagnosis by the Montreal Classification, which was not designed to assess the effect of smoking on need for surgery in IBD. Future studies

are necessary to validate that 40 years is the appropriate threshold for age at diagnosis. Also, IBD patients may have been misclassified and prevalent cases may have been labeled as incident. We defined incident IBD cases using a 3-year washout period in accordance with a case definition used in other studies of incident IBD in THIN.[22,26,27] To avoid misclassification, we additionally performed sensitivity analyses with a 5-year washout period. Our primary results did not change for Crohn's disease; however, the relationship between ex-smoking and colectomy was no longer significant for ulcerative colitis. Also, we *a priori* defined smoking status within 1 year of the index date. Due to the small number of patients who changed their smoking status after diagnosis of IBD, we were not able to analyze the effect of quitting smoking after diagnosis. Thus, our findings should be interpreted in the context of the effect of smoking at or near the diagnosis of IBD, and not by changes in smoking status after the diagnosis of IBD. In addition, we conducted a sensitivity analysis to assess the dose of smoking; however, we were unable to evaluate dose relative to duration of smoking because the start date of smoking was not reliably captured in the THIN database. Further, we did not assess for passive smoking exposure. Finally, we attempted to adjust for disease severity (e.g., including CRP and prednisone use at diagnosis), the influence of medical management (e.g., immunosuppressants before surgery), and disease duration. However, important clinical variables including disease extent and complications, such as strictures or abscesses are not reliably captured in the THIN database, and may represent residual confounding. Similarly, anti-tumor necrosis factor agents are not reliably recorded in THIN because specialist, rather than the general practitioner, primarily prescribe biologics. Because the THIN database lack these important clinical covariates, we encourage replication of our findings in other IBD databases.

Smoking is an important modifiable environmental risk factor of IBD. A novel finding of our study was that smoking at diagnosis was associated with an increased risk of surgery among older Crohn's disease patients. Quitting smoking was associated with an increased risk of colectomy among younger patients with ulcerative colitis; however, this finding was not substantiated by sensitivity analyses. Also, this is the first study to demonstrate that the prevalence of smoking among newly diagnosed patients with Crohn's disease is decreasing. Our data suggests that public health policy initiatives should be focused on primary prevention.

CONFLICT OF INTEREST

Guarantor of the article: Gilaad G. Kaplan, MD, MPH, FRCPC.

Specific author contributions: Study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript: Alexandra D. Frolkis; acquisition of data, analysis and interpretation of data, and critical revision of the manuscript: Mark Lowerison, Jordan Engbers, and Samuel Wiebe; interpretation of data and critical revision of the manuscript: Jennifer deBruyn, Nathalie Jette, William Ghali, Bertus Eksteen, Scott Patten, James Lewis, Isabelle Vallerand, Remo Panaccione, Subrata Ghosh, and Cheryl Barnabe; study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and study supervision: Gilaad G. Kaplan.

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Potential competing interests: None.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Over the past few decades, the prevalence of smoking in the general population has decreased in the UK.
- ✓ Smoking increases the risk of developing Crohn's disease and may increase the risk of intestinal resection.
- ✓ Individuals who quit smoking are at increased risk of developing ulcerative colitis and may be at increased risk of colectomy.

WHAT IS NEW HERE

- ✓ Patients newly diagnosed with Crohn's disease in 2009 were less likely to have a history of smoking as compared to those diagnosed in 1999.
- ✓ Among patients diagnosed with Crohn's disease after 40 years of age, current smokers were more likely to require surgery than non-smokers.
- ✓ Among patients diagnosed with ulcerative colitis between 17 and 40 years of age, former smokers were more likely to require colectomy than non-smokers.

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APPENDIX

Appendix 1

Crohn's disease and ulcerative colitis Read codes.

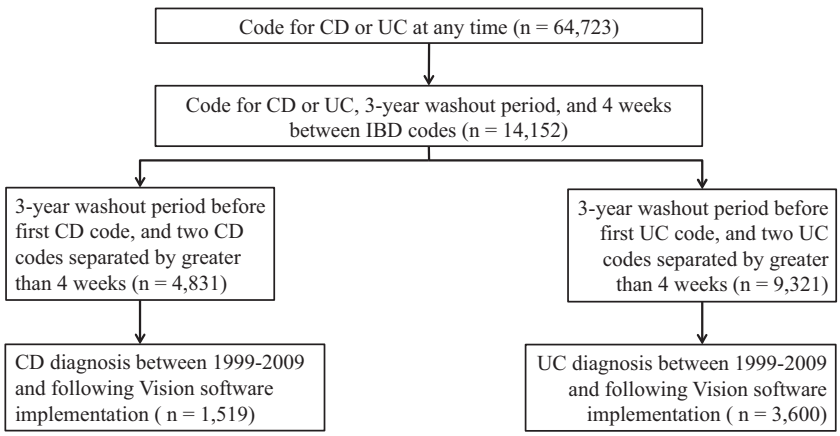
Code	Definition
Crohn's disease	
ZR3S.	Crohn's disease activity index/CDAI—Crohn's disease activity index
N0453	Juvenile arthritis in Crohn's disease
N0311	Arthropathy
Jyu40	[X]Other Crohn's disease
J08z9	Orofacial Crohn's disease
J40z.	Regional enteritis NOS/Crohn's disease NOS
J402.	Regional ileocolitis
J401z	Crohn's disease of the large bowel NOS/Crohn's colitis
J4012	Exacerbation of Crohn's disease of large intestine
J4011	Regional enteritis of the rectum

Appendix 1 *(Continued)*

Code	Definition
J4010	Regional enteritis of the colon
J401.	Regional enteritis of the large bowel
J400z	Crohn's disease of the small bowel NOS
J4005	Exacerbation of Crohn's disease of small intestine
J4004	Crohn's disease of the ileum NOS
J4003	Crohn's disease of the ileum unspecified
J4002	Crohn's disease of the terminal ileum
J4001	Regional enteritis of the jejunum
J4000	Regional enteritis of the duodenum
J400.	Regional enteritis of the small bowel
J40..	Regional enteritis-Crohn's disease/Crohn's disease/granulomatous enteritis
Ulcerative colitis	
14C4.	H/O: colitis / H/O: ulcerative colitis
N0310	Arthopathy in ulcerative colitis
N0454	Juvenille arthritis in ulcerative colitis
Jyu41	[X]Other ulcerative colitis
J41..	Idiopathic proctocolitis/ mucous colitis and/or proctitis/ ulcerative colitis and/or proctitis
J4...	Noninfective enteritis and colitis / colitis—noninfective / inflammatory bowel disease/ noninfective diarrhea
J41y.	Other idiopathic proctocolitis
J41yz	Other idiopathic proctocolitis NOS
J41z.	Idiopathic proctocolitis NOS
J412.	Ulcerative (chronic) ileocolitis
J411.	Ulcerative (chronic) enterocolitis
J410z	Ulcerative proctocolitis NOS
J4104	Exacerbation of ulcerative colitis
J4103	Ulcerative proctitis
J4102	Ulcerative rectosigmoiditis
J4101	Ulcerative colitis
J4100	Ulcerative ileocolitis
J410.	Ulcerative proctocolitis

Appendix 2

Flow diagram illustrating selection of the study population. CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.



Appendix 3

Surgery Read codes.

Code	Definition
7710.	Total excision of colon and rectum / panproctocolectomy / total proctocolectomy
7711z	Total excision of colon NOS
7712.	Extended excision of right hemicolon / extended right hemicolectomy
7713.	Other excision of right hemicolon / other right hemicolectomy
7714.	Excision of transverse colon / transverse colectomy
7715.	Excision of left hemicolon / left hemicolectomy

Appendix 3 *(Continued)*

Code	Definition
7716.	Excision of sigmoid colon / sigmoid colectomy
7717.	Other excision of colon / other colectomy
77100	Panproctocolectomy and ileostomy
77101	Panproctocolectomy anast ileum to anus and pouch creation HFQ / parks panproctocolectomy, ileoanal anastom and creation pouch
77102	Panproctocolectomy and anastomosis of ileum to anus NEC
77103	Proctocolectomy NEC
7710y	Other specified total excision of colon and rectum
7710z	Total excision of colon and rectum NOS
7711y	Other specified total excision of colon
77112	Total colectomy and ileostomy NEC
77111	Total colectomy, ileostomy and creation of rectal fistula HFQ
77110	Total colectomy and anastomosis of ileum to rectum / Hampton ileo-rectal anastomosis
7711.	Total excision of colon / total colectomy
77120	Extended right hemicolectomy and end to end anastomosis
77121	Extended right hemicolectomy and anastomosis ileum to colon
77122	Extended right hemicolectomy and anastomosis NEC
77123	Extended right hemicolectomy and ileostomy HFQ
7712y	Other specified extended excision of right hemicolon
7712z	Extended excision of right hemicolon NOS
77130	Right hemicolectomy+end to end anastomosis of ileum to colon / Ileocaecal resection
77131	Right hemicolectomy+side to side anast ileum to transv colon
77132	Right hemicolectomy and anastomosis NEC
77133	Right hemicolectomy and ileostomy however further qualified
7713y	Other specified other excision of right hemicolon
7713z	Other excision of right hemicolon NOS
77140	Transverse colectomy and end to end anastomosis
77141	Transverse colectomy and anastomosis of ileum to colon
77142	Transverse colectomy and anastomosis NEC
77143	Transverse colectomy and ileostomy HFQ
77144	Transverse colectomy and exteriorisation of bowel NEC
7714y	Other specified excision of transverse colon
7714z	Excision of transverse colon NOS
77150	Left hemicolectomy+end to end anastomosis of colon to rectum
77151	Left hemicolectomy+end to end anastomosis of colon to colon
77152	Left hemicolectomy and anastomosis NEC
77153	Left hemicolectomy and ileostomy however further qualified
77154	Left hemicolectomy and exteriorisation of bowel NEC
7715y	Other specified excision of left hemicolon
7715z	Excision of left hemicolon NOS
77160	Sigmoid colectomy+end to end anastomosis of ileum to rectum
77161	Sigmoid colectomy and anastomosis of colon to rectum
77162	Sigmoid colectomy and anastomosis NEC
77163	Sigmoid colectomy and ileostomy however further qualified
77164	Sigmoid colectomy and exteriorisation of bowel NEC
7716y	Other specified excision of sigmoid colon
7716z	Excision of sigmoid colon NOS
77170	Colectomy and end to end anastomosis of colon to colon NEC
77171	Colectomy and side to side anastomosis of ileum to colon NEC
77172	Colectomy and anastomosis NEC
77173	Colectomy and ileostomy NEC
77174	Colectomy and exteriorisation of bowel NEC / Mikulicz colectomy and colostomy / Paul colectomy and colostomy
77175	Partial colectomy NEC
7717y	Other specified other excision of colon
7717z	Other excision of colon NOS / colectomy NEC / hemicolectomy NEC / Rankin partial colectomy
76400	Ileectomy and anastomosis of stomach to ileum
76401	Ileectomy and anastomosis of duodenum to ileum
76402	Ileectomy and anastomosis of ileum to ileum
76403	Ileectomy and anastomosis of ileum to colon
7640y	Other specified excision of ileum
7640z	Excision of ileum NOS / Ileectomy NEC
7640.	Excision of ileum / Ileectomy
7630.	Excision of jejunum / jejunectomy
76300	Total jejunectomy and anastomosis of stomach to ileum
76301	Total jejunectomy and anastomosis of duodenum to ileum
76302	Total jejunectomy and anastomosis of duodenum to colon
76303	Partial jejunectomy and anastomosis of jejunum to ileum
76304	Partial jejunectomy and anastomosis of duodenum to colon
7630y	Other specified excision of jejunum
7630z	Excision of jejunum NOS
7620.	Excision of duodenum / duodenectomy
77212	Anterior resection rectum+staple anastomosis colon-rectum
77213	Anterior resection of rectum and anastomosis NEC
77214	Anterior resection of rectum and exteriorisation of bowel

Appendix 4

A total of 1-, 3-, and 5-year risk of surgery stratified by age at diagnosis for Crohn's disease and ulcerative colitis.

	Crohn's disease		Ulcerative colitis	
	Cumulative risk of surgery (95% CI), 17–40 years old, ($n=1008$)	**Cumulative risk of surgery (95% CI), >40 years old, ($n=511$)**	**Cumulative risk of surgery (95% CI), 17–40 years old, ($n=1672$)**	**Cumulative risk of surgery (95% CI), >40 years old, ($n=1928$)**
1-year risk (%)	8.61 (7.02–10.54)	4.63 (3.10–6.88)	2.85 (2.15–3.77)	1.52 (1.06–2.18)
3-year risk (%)	13.67 (11.65–16.01)	9.76 (7.42–12.78)	5.47 (4.45–6.70)	4.20 (3.37–5.23)
5-year risk (%)	17.95 (15.54–20.69)	11.61 (8.95–14.98)	7.61 (6.33–9.12)	5.97 (4.93–7.22)