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’s 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. Most patients with IBD are prescribed medications to control disease activity, 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. The 10-year risk of intestinal resection is 47 and 16% for Crohn’s disease and ulcerative colitis, respectively.

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

As advances in medical management have likely accounted for the reduced risk of surgery in IBD, 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. In 1980, 39% of UK adults smoked, whereas in 2010 this percentage decreased to 20%. 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. Patients registered in THIN are nationally representative and have a similar age, sex, and mortality distribution to that of the general UK population. 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-1980s. It is used to capture demographic data, medical diagnoses (in the form of Read codes), prescriptions, and laboratory data.

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. Furthermore, studies of the General Practice Research Database and THIN have demonstrated that both databases have similar validity in data recording. A validated list of Read codes was used to identify adults with Crohn's disease and ulcerative colitis (Appendix 1). 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. 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; (2) had two or more codes for Crohn's disease or ulcerative colitis recorded, separated by a time interval of at least 4 weeks; (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. 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. (1) 17–40 years and (2) >40 years. Corticosteroid at diagnosis was explored as a marker for disease severity. The primary exposure for 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. Immunosuppressant use (azathioprine, 6-mercaptopurine, and methotrexate) was defined as immunosuppressant use for greater than 6 months before surgery. In a secondary analysis, the role of C-reactive protein (CRP) was explored as a marker of disease activity. 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.

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).

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, 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: 3.00–3.00).

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| 25.5                    | 22.1                      |
| **Medications** |                       |                           |
| Corticosteroid| 37.4                    | 45.1                      |
| Immunomodulator| 31.7                   | 18.4                      |
| C-reactive protein |               |                           |
| <10 mg/l      | 63.4                    | 77.8                      |
| ≥10 mg/l      | 36.6                    | 22.2                      |
| **Disease duration** |             |                           |
| Median (Q1, Q3) | 4.6 (2.7, 7.4)       | 5.4 (3.2, 7.9)             |

*Patients were smokers; however, we were unable to classify as current- or ex-smoker at diagnosis of Crohn’s disease.

bCorticosteroid use within 90 days of index.

cImmunomodulator use for 6 months before surgery, but does not include anti-tumor necrosis factor therapies.

dC-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).

*Years from disease diagnosis until first surgery or study end.
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).

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

| Smoking | 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 |
| **Never-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) |
| Ex-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) |
| Current-smoker | | | |

| Sex | 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 |
| **Female** | 1.14 (0.80–1.62) | 1.10 (0.59–2.06) | 1.12 (0.76–1.64) | 1.95 (1.21–3.15) |
| Male | 1.52 (1.07–2.15) | 2.21 (1.18–4.12) | 1.84 (1.25–2.73) | 2.38 (1.48–3.81) |

| Corticosteroid | Crohn’s disease | Ulcerative colitis |
|---------------|-----------------|-------------------|
|               | 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 |
| **No** | 0.52 (0.35–0.77) | 0.58 (0.26–1.27) | 0.63 (0.39–1.01) | 1.46 (0.87–2.44) |
| Yes | 1.51 (0.90–2.53) | 2.65 (1.24–5.67) | 1.09 (0.63–1.86) | 1.09 (0.63–1.86) |

| Immunosuppressant | Crohn’s disease | Ulcerative colitis |
|------------------|-----------------|-------------------|
|               | Hazard ratio (95% CI), 17–40 years old, current- vs. never-smoker | Hazard ratio (95% CI), > 40 years old, ex-smoker vs. never-smoker |
| **No** | 0.87 (0.62–1.23) | 2.95 (1.56–5.58) | 1.12 (0.75–1.67) | 1.41 (0.94–2.14) |
| Yes | 0.55 (0.55–1.30) | 3.16 (1.58–6.32) | 1.58 (0.97–2.57) | 1.20 (0.72–1.97) |

**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

| Smoking | Crohn’s disease | Ulcerative colitis |
|---------|-----------------|-------------------|
|         | Hazard ratio (95% CI), 17–40 years old, current- vs. never-smoker | Hazard ratio (95% CI), > 40 years old, ex-smoker vs. never-smoker |
| **Subset of patients with CRP** | 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 | 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** | 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 interval; CRP, C-reactive protein; IBD, inflammatory bowel disease.

*Referent.

*Includes IBD patients who smoked, but were not classified as current or ex-smokers at the index date.

**Minimum registry in THIN for 5 years before index.
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.\(^ {3}\) 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.\textsuperscript{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 lacks 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, FRCP.

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                                                                 |
|--------|---------------------------------------------------------------------------|
| ZR35   | Crohn’s disease activity index/CDAI—Crohn’s disease activity index         |
| N0453  | Juvenile arthritis in Crohn’s disease                                      |
| N0311  | Arthropy                                                                   |
| Jy40   | [X]Other Crohn’s disease                                                  |
| J0529  | Orofacial Crohn’s disease                                                  |
| J402Z  | 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                                          |

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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                           |
| 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

| Code   | Definition                                                                                          |
|--------|------------------------------------------------------------------------------------------------------|
| 14C4.  | H/O: colitis / H/O: ulcerative colitis                                                               |
| N0310  | Arthopathy in ulcerative colitis                                                                   |
| N0454  | Juvenile arthritis in ulcerative colitis                                                             |
| Jyu41  | Ileitis of distal colon and ileitis                                                                 |
| J41..  | Idiopathic proctocolitis/mucous colitis and/or proctitis/ulcerative colitis and/or proctitis         |
| J41y.  | Other idiopathic proctocolitis                                                                      |
| J41yz. | Other idiopathic proctocolitis NOS                                                                   |
| J41z.  | Idiopathic proctocolitis NOS                                                                       |
| J412.. | Ulcerative (chronic) ileocolitis                                                                   |
| J411.. | Ulcerative (chronic) enterocolitis                                                                  |
| J410.. | Ulcerative proctocolitis NOS                                                                       |
| J4104  | Exacerbation of ulcerative colitis                                                                  |
| J4103  | Ulcerative proctitis                                                                                 |
| J4102  | Ulcerative rectosigmoiditis                                                                         |
| J4101  | Ulcerative proctitis                                                                                |
| 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                                                      |
| 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                                                                                           |
| 7711y    | Other specified total excision of colon                                                                                                       |
| 77112    | Total colectomy and ileostomy NEC                                                                                                             |
| 77111    | Total colectomy, ileostomy and creation of rectal fistula HFQ                                                                                  |
| 77153    | Total colectomy and anastomosis of ileum to rectum / Hampton ileo-rectal anastomosis                                                          |
| 771.     | Total excision of colon / total colectomy                                                                                                     |
| 77120    | Extended right hemicolecotomy and end to end anastomosis                                                                                      |
| 77121    | Extended right hemicolecotomy and anastomosis ileum to colon                                                                               |
| 77122    | Extended right hemicolecotomy and anastomosis NEC                                                                                             |
| 7712y    | Other specified extended excision of right hemicolon                                                                                          |
| 7712z    | Extended excision of right hemicolon NOS                                                                                                     |
| 77130    | Right hemicolecotomy+end to end anastomosis of ileum to colon / Ileocaecal resection                                                       |
| 77131    | Right hemicolecotomy+side to side anast ileum to transv colon                                                                               |
| 77132    | Right hemicolecotomy and anastomosis NEC                                                                                                     |
| 77133    | Right hemicolecotomy 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    | Other specified excision of ileum                                                                                                            |
| 77150    | Left hemicolecotomy+end to end anastomosis of colon to rectum                                                                               |
| 77151    | Left hemicolecotomy+end to end anastomosis of colon to colon                                                                               |
| 77152    | Left hemicolecotomy and anastomosis NEC                                                                                                       |
| 77153    | Left hemicolecotomy and ileostomy however further qualified                                                                                 |
| 77154    | Left hemicolecotomy 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 / hemicolecotomy 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 | Cumulative risk     |
|                      | (95% CI), 17–40 years old, (n = 1008) | (95% CI), > 40 years old, (n = 511) | Cumulative risk (95% CI), 17–40 years old, (n = 1672) | Cumulative risk (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 (7.42–12.76)  | 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) |