Gastroenterology Report, 6(4), 2018, 263–269

doi: 10.1093/gastro/goy030
Advance Access Publication Date: 13 August 2018
Original article

ORIGINAL ARTICLE

Colorectal cancer resection rates in patients with inflammatory bowel disease: a population-based study

Udayakumar Navaneethan[1,*], Xiang Zhu[1], Dennisdhilak Lourdusamy[1], Vennisvasanth Lourdusamy[1], Bo Shen[2] and Ravi Kiran[3]

[1]Center for Interventional Endoscopy, Florida Hospital, Orlando, FL 32803, USA, [2]Center for Inflammatory Bowel Diseases, The Cleveland Clinic, Cleveland, OH 44195, USA and [3]Division of Colorectal Surgery, Columbia University Medical Center/New York Presbyterian Hospital, New York, NY 10032, USA

*Corresponding author. Center for Interventional Endoscopy, Florida Hospital, University of Central Florida College of Medicine, 601 E Rollins Street, Orlando, FL 32803, USA. Tel: +1-216 502 0981; Fax: +1-407-303-2585; Email: udhaykumar81@gmail.com

Abstract

Background and objective: Inflammatory bowel disease (IBD) is associated with an increased risk of colorectal cancer (CRC). This study aimed to analyse the trends in rates of resection for IBD-related CRC in the USA.
Methods: We used the Nationwide Inpatient Sample from 1995 to 2012. Temporal trends in age-adjusted rates of resection for CRC in the setting of IBD were analysed using multivariate Joinpoint regression models. The primary outcome was surgical resection of CRC in the setting of IBD.
Results: We included 3 597 168 IBD discharges in the present study, of which 275 479 underwent CRC resection between 1995 and 2012. The annual CRC resection rates among IBD population decreased significantly from 1995 to 2012. This decrease was significant in all age groups with an annual decrease of 393 ($P < 0.001$), 359 ($P < 0.001$), 293 ($P < 0.001$) and 159 ($P < 0.001$) per 100 000 IBD discharges between 1995 and 2012 for age groups 18–39, 40–49, 50–74 and >75 years, respectively. The annual IBD-CRC resection rate per 100 000 IBD discharges for proximal CRC decreased by 149 ($P < 0.001$), 130 ($P < 0.001$), 95 ($P < 0.001$) and 50 ($P < 0.001$), respectively, and the annual distal CRC resections per 100 000 IBD discharges decreased by 104 ($P < 0.001$), 123 ($P < 0.001$), 123 ($P < 0.001$) and 82 ($P < 0.001$), respectively, for age groups 18–39, 40–49, 50–74 and >75 years, between 1995 and 2012. On multivariate Poisson regression analysis, after adjustment for age and sex, CRC resections decreased by 3.9% each year from 1995 to 2012.
Conclusions: CRC resection rates among IBD patients have continued to decrease annually from 1995 to 2012. There is a population-level decrease in resection of both proximal and distal CRC reflecting a decreasing incidence of IBD-related CRC incidence in the USA.

Key words: Colorectal cancer; inflammatory bowel disease; Crohn's disease; ulcerative colitis; surgery

Introduction

Inflammatory bowel disease (IBD) including ulcerative colitis (UC) and Crohn's disease (CD) are chronic bowel disease with a clinical course marked by exacerbations and remissions and an increased risk of colorectal cancer (CRC) [1–4]. The association of IBD with the risk of CRC has led to the North American

Submitted: 14 March 2018; **Revised:** 28 April 2018; **Accepted:** 16 July 2018

consensus statement, which recommends regular surveillance with colonoscopy every 1–2 years for UC or CD patients with colonic disease for 8 years [1]. During the past two decades, a tremendous evolution in the treatment strategy of IBD patients with the introduction of biologic agents such as anti-tumor necrosis factor (TNF) agents modified the natural history of the disease process. In a large population-based study from Denmark, the risk of CRC associated with IBD has decreased with calendar time [5]. Although surveillance is recommended in IBD patients, the impact of this practice on CRC risk in IBD patients is not known. During the last two decades, the two major advances in the management of IBD were colonoscopic surveillance, which was introduced in 2000, and the use of biologics, which was introduced in 1998 [6]. We hypothesized that surveillance endoscopies along with advances in medical management protect against CRC and that surveillance endoscopies would impact on the risk of both proximal and distal CRC.

We examined the national trends in CRC resection rates in IBD patients in the USA and evaluated the influence of site of disease on these trends. We therefore conducted a trend analysis using the Nationwide Inpatient Sample (NIS) database between 1995 and 2012 and aimed to identify the temporal trends of the incidence and mortality of CRC in IBD patients in the context of surveillance colonoscopies and improvements in medical management.

Materials and methods

Data source

The data analysed in this study were obtained from the NIS database, which is the largest all-payer inpatient care database in the USA. The NIS database is developed for the Healthcare Cost and Utilization Project (HCUP); it represents approximately 20% of the stratified sample of US community hospitals, including all non-federal general and subspecialty hospitals, public hospitals and academic medical centers. The data include demographic variables (including age, sex, race/ethnicity), discharge disposition, primary and secondary diagnoses (up to 15), primary and secondary procedures (up to 15), primary insurance payers, total hospital charges and length of stay [7].

Study groups, definitions, inclusion and exclusion criteria

The NIS database was used to study all inpatient discharges that resulted in surgical resection of CRC for IBD between 1995 and 2012 [8]. We analysed the information of all adults aged 18 years or older at hospital admission. Trends were analysed for all adults and for different age subgroups: 18–39, 40–49, 50–74 and $\geq$75 years. Comorbid conditions were recorded if they were listed among the diagnoses for the hospitalization. The burden of comorbid illness was assessed based on the Deyo modification of the Charlson's Comorbidity Index (CCI) [9]. The CCI ranges from 0 to 17, with higher numbers representing a greater comorbidity burden. The CCI incorporates 17 comorbid conditions and has been shown to be a well-validated measure of comorbidity adjusting for disease burden in administrative data [9].

Outcomes

The primary outcome was surgical resection of CRC in the setting of IBD. A case of CRC resection was defined by a hospitalization including both an International Classification of Diseases, 9th revision, Clinical Modification procedure codes for colorectal resection surgery (17.31–17.36, 17.39, 45.71–45.76, 45.79, 45.8, 45.81–45.83, 48.40–48.43, 48.49, 48.5–48.52, 48.59, 48.61–48.65, 48.69) and/or a diagnosis code for malignant neoplasm of the colon (153.0–153.4, 153.6–153.9, 230.3), rectum (154.0, 154.1, 154.8, 230.4) or digestive system (235.2, 239.0) in the setting of IBD (556.X, 555.X). We adopted the ICD codes based on a previously published study [10]. Appropriate codes were used for each year studied by using the conversion table provided by the Centers for Disease Control and Prevention [10].

Since most patients undergo complete proctocolectomy for CRC in the setting of IBD, the differentiation of proximal and distal CRC was defined based on the diagnosis codes [10]. However, studies using the SEER (Surveillance, Epidemiology and End Results) database of CRC in the setting of IBD demonstrated that only 6% of patients with IBD-associated CRC underwent total proctocolectomy and the rest underwent segmental colectomy [11]. Additionally, proximal CRC was defined by procedure codes for laparoscopic or open surgical resection proximal to but not including the splenic flexure (17.32–17.34, 45.72–45.74), whereas distal CRC was defined by procedure codes for laparoscopic or open surgical resection including the splenic flexure, descending, sigmoid colon or rectum (17.35, 17.36, 45.75, 45.76, 48.40–48.43, 48.49, 48.5–48.52, 48.59, 48.61–48.65, 48.69). When the procedure code did not specify anatomic site, the anatomic site was defined by the diagnosis code.

The NIS database consists of de-identified data with no risk of loss of confidentiality. The present study was exempt from Florida Hospital Institutional Review Board review. The data user agreement was completed with the Agency for Healthcare Research and Quality before using the NIS database.

Statistical analysis

All statistical analyses were performed using the Stata 14.0 software package (Stata Corp LP, College Station, TX) to adjust for the complex sampling design of the NIS database. To examine trends in CRC resection from 1995 to 2012, and to allow comparisons between demographic subgroups based on age and sex, national estimates of direct age-adjusted CRC resection rates and 95% confidence intervals (CIs) were calculated for each year of the study period for all adults, and were stratified by age group and sex. Resection rates were calculated for CRC overall, which includes proximal and distal CRC, and then separately for proximal and distal CRC and after adjustment for CCI.

Population data from the US Bureau of the Census were used to calculate direct age-adjusted resection rates per 100 000 persons for every study year, using the year 2000 US standard population as the reference standardizing population [12]. All results reported were age-adjusted resection rates, standardized to the year 2000 US standard population.

Trends in age-adjusted CRC resection rates over time were analysed using Joinpoint trend analysis software version 3.5.2 from the SEER program of the National Cancer Institute [13].

Results

IBD population

The information of 3 597 168 IBD patients who were discharged between 1995 and 2012 was estimated in the present study. Among them, male and female IBD patients were 1 518 725 (42.2%) and 2 078 443 (57.8%), respectively. The mean age of the

IBD patients was 51.6 years. The total number of IBD patients in age groups 18–39, 40–49, 50–74 and >75 years were 1 120 984 (31.2%), 607 586 (16.9%), 1 321 947 (36.8%) and 546 651 (15.2%), respectively. The CRC resection was performed in 275 479 (7.7%) of the total IBD discharges. Among the IBD discharges, CD and UC discharges accounted for approximately 63 and 37%, respectively (Table 1).

Table 1. Summary of demographic characteristics of all IBD patients discharged between 1995 and 2012

Demographics characteristic	IBD ($n = 3\,597\,168$)	CD[b] ($n = 2\,288\,107$)	UC[b] ($n = 1\,333\,275$)
Age (years)[a]	51.6 (19.1)	49.6 (18.4)	55.1 (19.8)
Age group			
18–39 years	1 120 984 (31.2)	780 647 (34.1)	350 078 (26.3)
40–49 years	607 586 (16.9)	420 581 (18.4)	191 238 (14.3)
50–74 years	1 321 947 (36.8)	814 972 (35.6)	514 645 (38.6)
>75 years	546 651 (15.2)	271 907 (11.9)	277 314 (20.8)
Sex			
Male	1 518 725 (42.2)	918 103 (40.1)	611 520 (45.9)
Female	2 078 443 (57.8)	1 370 004 (59.9)	721 755 (54.1)
CRC resection	275 479 (7.7)	162 933 (7.1)	116 055 (8.7)
Distal CRC resection	103 148 (2.9)	38 839 (1.7)	65 964 (4.9)
Proximal CRC resection	12 728 (0.4)	116 102 (5.1)	12 182 (0.9)
CCI[a]	0.81 (1.49)	0.73 (1.40)	0.94 (1.61)
CCI for distal CRC[a]	0.67 (1.57)	0.62 (1.49)	0.69 (1.61)
CCI for proximal CRC[a]	0.49 (1.39)	0.40 (1.25)	1.37 (2.18)

[a]These values are presented as mean ± standard deviation; other values are presented as number of cases followed by percentage in parentheses.
[b]Because some of discharges were identified as both CD and UC in the diagnosis coding, these discharges were repeatedly counted and therefore the sum of CD and UC was greater than the total number of IBD discharges.
IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; CRC, colorectal cancer; CCI, Charlson's Comorbidity Index.

IBD discharge rates for different age groups

The overall IBD discharge rates significantly increased annually from 1995 to 2012. With age adjustment, overall IBD discharge rates in the USA increased from 59.76 (95% CI, 59.41–60.11) per 100 000 persons in 1995 to 131.64 (95% CI, 131.11–132.17) per 100 000 persons, with an annual increase of 4.23 per 100 000 persons. When stratified based on age, there was a significant increase in the IBD discharge rates in all age groups from 1995 to 2012, with the age group >75 years having the highest increase and the age group 18–39 years having the lowest increase. In age group >75 years, IBD discharge rates increased from 113.52 (95% CI, 111.78–115.26) per 100 000 persons in 1995 to 245.13 (95% CI, 242.66–247.60) per 100 000 persons in 2012, with an annual increase of 7.74 (95% CI, 5.05–10.44) per 100 000 persons. In the age group 18–39 years, the IBD discharge rates increased from 48.64 (95% CI, 48.15–49.13) per 100 000 persons in 1995 to 93.01 (95% CI, 92.34–93.68) per 100 000 persons in 2012, with an annual increase of 2.61 (95% CI, 1.49–3.73) per 100 000 persons.

IBD discharges among men increased by 2.4 ($P < 0.001$), 2.4 ($P < 0.001$), 5.6 ($P < 0.001$) and 6.2 ($P < 0.001$) per 100 000 persons annually between 1995 and 2012 for age groups 18–39, 40–49, 50–74 and >75 years, respectively. IBD discharges among women increased by 2.8 ($P < 0.001$), 3.6 ($P < 0.001$), 7.3 ($P < 0.001$) and 9.2 ($P < 0.001$) per 100 000 persons annually in the same period for age groups 18–39, 40–49, 50–74 and >75 years, respectively (Supplementary Table 1).

CRC resection rates in the IBD population

Rates of discharge following CRC resection per 100 000 IBD discharges from 1995 and 2012 demonstrated a significant decrease in all the age groups (Table 2).

Table 2. Temporal trend in CRC discharge rates per 100 000 IBD patients in different age groups

Group	Discharge rate per 100 000 IBD patients (95% CI)		Annual change (95% CI)
	1995	2012	1995–2012
All adults (>18 years)			
Age-adjusted CRC	11 798.11 (11 609.01–11 987.21)	6052.82 (5955.11–6150.53)	−337.96 (−387.61–288.3)
Age-adjusted PCRC resection	5085.15 (4955.99–5214.31)	3016.65 (2944.91–3088.39)	−121.68 (−150.27–93.09)
Age-adjusted DCRC resection	4042.11 (3932.13–4152.09)	2144.23 (2084.31–2204.15)	−111.64 (−136.02–87.26)
Patients aged 18–39 years			
CRC	13 389.96 (13 059.43–13 720.49)	6710.04 (6535.62–6884.46)	−392.94 (−460–325.87)
PCRC resection	6622.75 (6382.32–6863.18)	4093.35 (3954.66–4232.04)	−148.79 (−191.26–106.32)
DCRC resection	4041.63 (3857.59–4225.67)	2275.69 (2170.28–2381.1)	−103.88 (−139.39–68.37)
Patients aged 40–49 years			
CRC	12 005.93 (11 575.14–12 436.72)	5910.56 (5681.3–6139.82)	−358.55 (−418.15–298.95)
PCRC resection	4967.1 (4681–5253.2)	2748.76 (2592.63–2904.89)	−130.49 (−167.74–93.24)
DCRC resection	4320.11 (4067.74–4572.48)	2230.57 (2083.55–2377.59)	−122.91 (−150.86–94.97)
Patients aged 50–74 years			
CRC	10 812.88 (10 511.71–11 114.05)	5830.88 (5690.09–5971.67)	−293.06 (−332.49–253.63)
PCRC resection	3771.92 (3593.7–3950.14)	2150.9 (2065.25–2236.55)	−95.35 (−111.4–79.31)
DCRC resection	4268.34 (4078.53–4458.15)	2180.39 (2094.91–2265.87)	−122.82 (−141.81–103.83)
Patients aged >75 years			
CRC	6495.97 (6149.52–6842.42)	3784.87 (3596.24–3973.5)	−159.48 (−179.81–139.14)
PCRC resection	2051.04 (1851.06–2251.02)	1193.14 (1083.62–1302.66)	−50.46 (−67.18–33.75)
DCRC resection	2437.25 (2217.49–2657.01)	1046.51 (937.93–1155.09)	−81.81 (−99.76–63.86)

IBD, inflammatory bowel disease; CRC, colorectal cancer; CI, confidence interval; PCRC, proximal colorectal cancer; DCRC, distal colorectal cancer.

The annual decrease in CRC resections in IBD discharges was significant in all age groups with decreases of 392.94 ($P < 0.001$), 358.55 ($P < 0.001$), 293.06 ($P < 0.001$) and 159.48 ($P < 0.001$) per 100 000 IBD patients annually between 1995 and 2012 for age groups 18–39, 40–49, 50–74 and > 75 years, respectively (Table 2). Figure 1A demonstrates the decrease in CRC resections in IBD patients in all age groups.

We classified CRC resection in IBD discharges based on underlying diagnosis of UC and CD and found a similar annual decrease in CRC resections of both proximal and distal colon cancer in UC and CD discharges (Supplementary Tables 2 and 3).

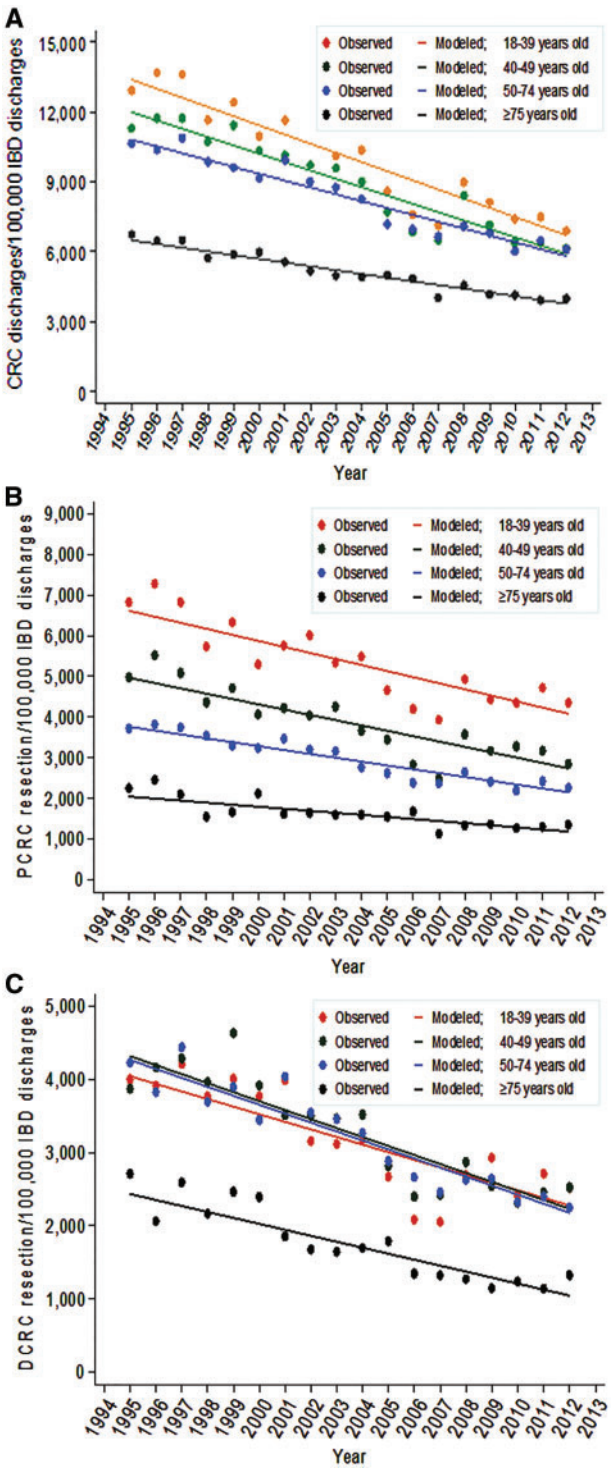

Figure 1. Temporal trends in colorectal cancer (CRC) resection rates in inflammatory bowel disease (IBD) patients in different age groups. CRC (**A**), proximal CRC (PCRC) (**B**) and distal CRC (DCRC) (**C**) resection rates show significant decreases in all age groups.

Trends in proximal and distal CRC resection rates

The proximal and distal CRC resection rates per 100 000 IBD discharges showed a significant decrease between 1995 and 2012. The annual proximal CRC resection rate per 100 000 IBD discharges decreased by 148.79 ($P < 0.001$), 130.49 ($P < 0.001$), 95.35 ($P < 0.001$) and 50.46 ($P < 0.001$) for age groups 18–39, 40–49, 50–74 and >75 years, respectively, between 1995 and 2012. The annual distal CRC resections per 100 000 IBD discharges decreased for all age groups 18–39, 40–49, 50–74 and >75 years between 1995 and 2012 (Table 2). Age-adjusted proximal and distal CRC resections among IBD discharges decreased annually between 1995 and 2012 (Table 2; Figure 1B and C).

CRC resection rates in men and women

The CRC resection rates were also analysed for men and women separately. CRC resections for male IBD patients decreased by 412.81 ($P < 0.001$), 380.17 ($P < 0.001$), 299.05 ($P < 0.001$) and 147.32 ($P < 0.001$) per 100 000 IBD discharges annually between 1995 and 2012 for age groups 18–39, 40–49, 50–74 and >75 years, respectively (Table 3). CRC resections for female IBD discharges decreased by 383.55 ($P < 0.001$), 336.56 ($P < 0.001$), 286.81 ($P < 0.001$) and 167.63 ($P < 0.001$) per 100 000 IBD discharges annually in the same period for age groups 18–39, 40–49, 50–74 and >75 years, respectively (Table 4).

The proximal and distal CRC resections per 100 000 IBD discharges in both men and women also significantly decreased in all age groups (all $P < 0.001$; Tables 3 and 4). Age-adjusted proximal and distal CRC resections in IBD patients decreased separately by 115.8 ($P < 0.001$) and 128.8 ($P < 0.001$) per 100 000 IBD discharges in men, and decreased separately by 140.6 ($P < 0.001$) and 104.8 ($P < 0.001$) in women, annually between 1995 and 2012 (Supplementary Tables 4 and 5).

We adjusted CCI in analysing the trend in CRC resection rates and demonstrated that the CCI has remained unchanged during the study period when significant decreases in CRC resection rates were observed. Figure 2A demonstrates the age-adjusted CRC discharge rate per 100 000 IBD patients between 1995 and 2012. There was a significant decrease in CRC resection rates in contrast with the unchanged CCI during the same period. Figure 2B and C demonstrates the age-adjusted proximal and distal CRC resection rates per 100 000 IBD patients between 1995 and 2012. There was a significant decrease in CRC resection rates in contrast with the unchanged CCI during the same period.

Multivariate Poisson regression

On multivariate Poisson regression analysis, after adjustment for age and sex, CRC resections per 100 000 IBD discharges decreased by 3.9% each year. CRC resections decreased by 21.5% in women compared to men. Also, the incidence risk ratio demonstrated that, for every increase in age group (18–39, 40–49, 50–74 and >75 years), the CRC resections per 100 000 IBD discharges decreased by 17.7% (Table 5).

Table 3. Temporal trend in CRC discharge rates per 100 000 IBD patients in different age groups among male patients

Group	Discharge rate per 100 000 IBD discharges (95% CI)		Annual change (95% CI)
	1995	2012	1995–2012
All men (>18 years)			
Age-adjusted CRC	13 280.50 (12 967.57–13 593.43)	7299.15 (7136.98–7461.32)	−351.84 (−414.06–289.62)
Age-adjusted PCRC resection	5315.73 (5108.52–5522.94)	3347.97 (3233.74–3462.20)	−115.75 (−149.34–82.16)
Age-adjusted DCRC resection	4825.80 (4638.38–5013.22)	2636.57 (2536.04–2737.10)	−128.78 (−156.83–100.73)
Male patients aged 18–39 years			
CRC	15 265.17 (14 714.49–15 815.85)	8247.35 (7961.72–8532.98)	−412.81 (−499.87–325.76)
PCRC resection	7186.5 (6795.83–7577.17)	4696.96 (4475.23–4918.69)	−146.44 (−199.24–93.64)
DCRC resection	4871.69 (4554.31–5189.07)	2821.19 (2648.59–2993.79)	−120.62 (−163.75–77.48)
Male patients aged 40–49 years			
CRC	13 609.11 (12 879.32–14 338.9)	7146.3 (6751.97–7540.63)	−380.17 (−462.02–298.31)
PCRC resection	4872.57 (4395.98–5349.16)	2872.09 (2621.15–3123.03)	−117.68 (−179.06–56.29)
DCRC resection	5397.04 (4962.02–5832.06)	2799.95 (2541.50–3058.40)	−152.77 (−192.12–113.42)
Male patients aged 50–74 years			
CRC	11 973.32 (11 497.98–12 448.66)	6889.43 (6659.05–7119.81)	−299.05 (−343.86–254.25)
PCRC resection	3669.86 (3417.78–3921.94)	2299.3 (2169.61–2428.99)	−80.62 (−97.66–63.58)
DCRC resection	4977.27 (4664.53–5290.01)	2673.18 (2528.59–2817.77)	−135.53 (−161.66–109.41)
Male patients aged >75 years			
CRC	6678.62 (6085.94–7271.3)	4174.27 (3848.28–4500.26)	−147.32 (−185.12–109.51)
PCRC resection	2219.67 (1866.99–2572.35)	1276.63 (1090.27–1462.99)	−55.47 (−77.65–33.3)
DCRC resection	2251.63 (1881.48–2621.78)	1039.44 (864.63–1214.25)	−71.30 (−98.48–44.13)

IBD, inflammatory bowel disease; CRC, colorectal cancer; CI, confidential interval; PCRC, proximal colorectal cancer; DCRC, distal colorectal cancer.

Table 4. Temporal trend in CRC discharge rates per 100 000 IBD patients in different age groups among female patients

Group	Discharges rate per 100 000 IBD discharges (95% CI)		Annual change (95% CI)
	1995	2012	1995–2012
All women (>18 years)			
Age-adjusted CRC	10 694.24 (10 460.27–10 928.21)	5109.22 (4989.19–5229.25)	−328.53 (−373.46–283.60)
Age-adjusted PCRC resection	5285.62 (5120.82–5450.42)	3074.33 (2982.66–3166)	−140.57 (−169.82–111.32)
Age-adjusted DCRC resection	3659.7 (3527.87–3791.53)	1988.55 (1915.83–2061.27)	−104.78 (−127.93–81.64)
Women aged 18–39 years			
CRC	12 041.76 (11 634.94–12 448.58)	5521.39 (5305.16–5737.62)	−383.55 (−444.00–323.1)
PCRC resection	6721.06 (6418.24–7023.88)	4072.25 (3896.09–4248.41)	−170.95 (−211.12–130.78)
DCRC resection	3778.88 (3560.40–3997.36)	2237.51 (2106.82–2368.20)	−103.73 (−135.64–71.82)
Women aged 40–49 years			
CRC	10 757.29 (10 236.38–11 278.20)	5035.79 (4761.78–5309.80)	−336.56 (−390.93–282.18)
PCRC resection	4898.17 (4547.23–5249.11)	2668.49 (2469.75–2867.23)	−131.16 (−169.86–92.46)
DCRC resection	3490.07 (3189.86–3790.28)	1816.94 (1645.44–1988.44)	−98.42 (−126.87–69.97)
Women aged 50–74 years			
CRC	9878.57 (9492.39–10 264.75)	5002.86 (4828.58–5177.14)	−286.81 (−329.27–244.34)
PCRC resection	3820.15 (3570.58–4069.72)	2026.32 (1912.27–2140.37)	−105.52 (−132.69–78.35)
DCRC resection	3687.97 (3455.53–3920.41)	1794.06 (1692.28–1895.84)	−111.41 (−131.12–91.70)
Women aged >75 years			
CRC	6365.54 (5938.73–6792.35)	3515.89 (3286.82–3744.96)	−167.63 (−190.57–144.69)
PCRC resection	1932.23 (1690.48–2173.98)	1122.81 (988.20–1257.42)	−47.61 (−63.96–31.27)
DCRC resection	2511.53 (2238.35–2784.71)	1041.36 (902.79–1179.93)	−86.48 (−106.11–66.85)

IBD, inflammatory bowel disease; CRC, colorectal cancer; CI, confidential interval; PCRC, proximal colorectal cancer; DCRC, distal colorectal cancer.

Discussion

IBD is associated with an increased risk of CRC [1–4]. In our study, we analysed US trends in rates of resection for CRC for IBD, which may reflect CRC incidence. We observed that CRC resection rates in the IBD population have been steadily and significantly decreasing every year between 1995 and 2012. During the same period, there was a significant increase in IBD discharge rates per 100 000 persons. We also found that this decrease in CRC resection rates in the IBD population was consistent in the different age groups. On multivariate Poisson regression analysis, adjusting for age and sex, the CRC resection rates for the IBD population decreased significantly by 3.9% every year. Additionally, the CCI has not changed during the study period, highlighting that the decrease in CRC resection is not related to increasing comorbidities. This significant decrease in

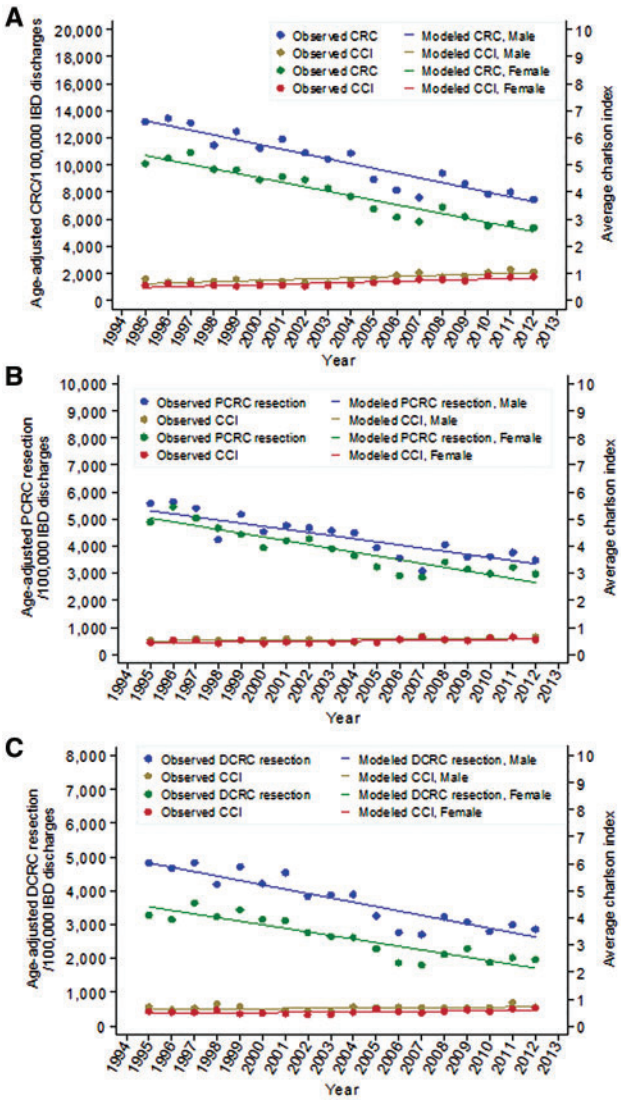

Figure 2. Temporal trends in the age-adjusted colorectal cancer (CRC) resection rates per 100 000 inflammatory bowel disease (IBD) patients over period between 1995 and 2012. There are significant decreases in CRC (**A**), proximal CRC (PCRC) (**B**) and distal CRC (DCRC) (**C**) resection rates in both male and female patients in contrast with the unchanged Charlson's Comorbidity Index (CCI) during the same period.

discharge rates was observed for both proximal and distal CRC. The CRC resection rates have decreased more in women than in men.

The CRC resection rates in the population maintained in the NIS database indirectly reflect the prevalence of CRC in the same population. Thus, this would suggest that the occurrence rate of CRC, in the proximal or distal colon, in IBD patients has significantly decreased over the past two decades. While colonoscopic screening and surveillance of IBD were introduced in 2000, biologics were introduced in 1998 [6]. We thus speculated that factors such as increased CRC surveillance screening and the extensive use of disease-modifying agents such as anti-TNF agents in the past decades could explain the decrease in the CRC incidence over these years.

Our observations are similar to the results of other large population-based studies from Europe that demonstrated a decreasing incidence of CRC in IBD patients [5, 14]. In a study of

Table 5. Multivariate Poisson regression models indicating that the IRR of IBD and CRC discharges is significantly associated with both age and year

Factor	IRR	95% CI	P-value
IBD discharges per 100 000 persons			
Age group	1.40	1.38–1.42	<0.0001
Year	1.05	1.05–1.05	<0.0001
Female	1.45	1.41–1.50	<0.0001
CRC discharges per 100 000 IBD patients			
Age group	0.82	0.82–0.82	<0.0001
Year	0.96	0.96–0.96	<0.0001
Female	0.78	0.78–0.79	<0.0001

With age increasing by one unit of age group, the CRC discharges decrease by 18%. If age and sex are under control, the CRC discharges per 100 000 IBD discharges decrease by 4% each year. Such CRC discharges decrease by 22% among women compared to men.
IBD, inflammatory bowel disease; CRC, colorectal cancer; IRR, incidence-rate ratio; CI, confidential interval.

7607 IBD patients (4125 with UC and 3482 with CD) diagnosed in Sweden from 1954 to 1989 and followed up through 2004, there was a substantial decrease over time in mortality from CRC, with a 70% decrease in the incidence of CRC between 1960 and 1969 and 2000 and 2004 [14]. Similarly, in a large population-based study of 47 374 IBD patients from Denmark, the risk of CRC associated with IBD decreased from 1979 to 2008 [5]. The decrease in risk of CRC over time may be related to changes in treatment and the incorporation of CRC surveillance in IBD patients. No changes in the surgical management of proximal versus distal CRC over the past two decades would explain the trends observed.

The observed trends in cancer incidence reflect changes in risk factors and employing preventive measures such as surveillance for dysplasia in IBD patients. Genetic factors are unlikely to impact on such a short time scale. A study demonstrated the impact of CRC surveillance in IBD patients in the USA over time [15]. Current American College of Gastroenterology practice guidelines recommend colonoscopic surveillance every 1–2 years for those with either UC or CD with colonic disease of 8-year duration for cancer surveillance [5]. Therefore, continued colonoscopic surveillance with early diagnosis of dysplastic lesions could also contribute to the lower incidence of CRC in the IBD population as observed in our present study. A similar trend in the decrease in colon cancer resection in both proximal and distal colon cancer has been reported in the general population also [10]. Incorporation of colonoscopy into the screening and surveillance algorithm has been suggested to explain this observation.

The chronic inflammatory process in the colonic mucosa in patients with IBD in addition to the genetic factors is thought to play a major role in carcinogenesis [16–18] and controlling the inflammatory process could halt this sequential process of inflammation-dysplasia-carcinoma. Biological agents have revolutionized the approach for IBD therapy in the past two decades [18]. Increased remission rates through the use of these agents and subsequent reduction in inflammation could also explain the reduction in the incidence of CRC in the past two decades [15]. However, the observed decrease in the incidence before biologics were introduced suggests that other factors may explain the decrease in the incidence of CRC. The other important contributing factor to the reduction in CRC over time could be attributed to the evolution of surgical thinking about

dysplasia over time. As the natural history of dysplasia became better known, colorectal surgeons had a shift in thinking from recommending surgeries for most of people with dysplasia to colonoscopy with surveillance in patients with low-grade dysplasia and indefinite dysplasia.

Our study had several limitations. First, the study data were collected and analysed in a retrospective manner using a deidentified database. This makes it impossible to validate individual ICD-9 codes. Nevertheless, the codes of colon cancer and their location have been validated [10]. Second, although the temporal trends in CRC resection have been analysed, other factors that could impact on the risks of CRC, including changes in use of medications with chemopreventive benefit such as nonsteroidal anti-inflammatory agents or statins, changes in the prevalence of other risk factors such as obesity and/or smoking and the development of high-definition endoscopy for identification of subtle lesions, cannot be entirely controlled. Third, a small proportion of patients could have had more than one CRC resection. Finally, there was a lack of laboratory data, use of medications such as biologics or statins and information on the duration of IBD diagnosis or disease distribution. Also, patients with asymptomatic IBD or limited disease extent IBD who had incidental CRC would be included in the study, as it was not possible to define symptoms based on the NIS database. There was also lack of information about the diagnosis of dysplasia in IBD patients. In spite of these limitations, this large population-based study clearly demonstrates a decreasing incidence of CRC in IBD patients in the USA.

Conclusions

CRC resection rate among IBD patients continued to significantly decrease annually in the USA between 1995 and 2012, with a reduction in the rates of resection of both proximal and distal CRC, which reflects a decrease in CRC incidence. Future prospective studies are required to understand the impact of the current practice and surveillance programs on overall outcome and survival of patients with IBD and CRC.

Acknowledgements

U.N., B.S. and R.K. conceived of this study; U.N. and R.K. conceived of the study design. X.Z., V.L. and D.L. prepared the manuscript and performed statistical analysis. U.N., B.S. and R.K. did critical revisions.

Supplementary data

Supplementary data is available at *Gastroenterology Report* online.

Conflict of interest statement: Udayakumar Navaneethan and Bo Shen are consultants for AbbVie. Udayakumar Navaneethan is on the speaker bureau for Takeda and a consultant for Janssen. None of the other authors declared financial conflict of interest.

References

1. Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010;**105**:501–23.
2. Jess T, Gamborg M, Matzen P *et al*. Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. *Am J Gastroenterol* 2005;**100**:2724–9.
3. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001;**48**:526–35.
4. Jess T, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. *Clin Gastroenterol Hepatol* 2012;**10**:639–45.
5. Jess T, Simonsen J, Jørgensen KT *et al*. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. *Gastroenterology* 2012;**143**:375–81.
6. Itzkowitz SH, Present DH. Crohn's and Colitis Foundation of America Colon Cancer in IBD Study Group. Consensus conference: colorectal cancer screening and surveillance in inflammatory bowel disease. *Inflamm Bowel Dis* 2005;**11**:314–21.
7. HCUP Nationwide Inpatient Sample (NIS). *Healthcare Cost and Utilization Project (HCUP)*. Rockville, MD: Agency for Healthcare Research and Quality, 1993–2012. www.hcup-us.ahrq.gov/nisoverview.jsp (10 January 2015, date last accessed).
8. Wingo PA, Guest JL, McGinnis L *et al*. Patterns of inpatient surgeries for the top four cancers in the United States, National Hospital Discharge Survey, 1988–95. *Cancer Causes Control* 2000;**11**:497–512.
9. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;**45**:613–9.
10. Myer PA, Mannalithara A, Singh G *et al*. Proximal and distal colorectal cancer resection rates in the United States since widespread screening by colonoscopy. *Gastroenterology* 2012;**143**:1227–36.
11. Gearhart SL, Nathan H, Pawlik TM *et al*. Outcomes from IBD-associated and non-IBD-associated colorectal cancer: a surveillance epidemiology and end results medicare study. *Dis Colon Rectum* 2012;**55**:270–7.
12. National Center for Health Statistics. *Post Censal Estimates of the Resident Population of the United States for July 1, 2000–July 1, 2009, by Year, County, Age, Bridged Race, Hispanic Origin, and Sex (Vintage 2009). Prepared under a Collaborative Arrangement with the US Census Bureau*. Released June 20, 2010. www.cdc.gov/nchs/nvss/bridged_race.htm (10 June 2017, date last accessed).
13. JoinPoint Regression Program, version 3.5–April 2011. Statistical Methodology and Applications Branch and Data Modeling Branch, Surveillance Research Program National Cancer Institute. http://surveillance.cancer.gov/joinpoint/ (10 January 2012, date last accessed).
14. Soderlund S, Brandt L, Lapidus A *et al*. Decreasing time-trends of colorectal cancer in a large cohort of patients with inflammatory bowel disease. *Gastroenterology* 2009;**136**:1561–7.
15. Lutgens MW, van Oijen MG, van der Heijden GJ *et al*. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. *Inflamm Bowel Dis* 2013;**19**:789–99.
16. Ullman TA, Itzkowitz SH. Intestinal inflammation and cancer. *Gastroenterology* 2011;**140**:1807–16.
17. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol* 2004;**287**:G7–17.
18. Rutter M, Saunders B, Wilkinson K *et al*. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004;**126**:451–9.