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Contemporary Risk of Surgery in Patients with Ulcerative Colitis and Crohn's Disease: A Meta-Analysis of Population-based Cohorts

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Abstract

Background: We conducted a systematic review with meta-analysis to estimate rates and trends of colectomy in patients with ulcerative colitis (UC), and of primary and re-resection in patients with Crohn's disease (CD), focusing on contemporary risks.

Methods: Through a systematic review till September 3, 2019, we identified population-based cohort studies that reported patient-level cumulative risk of surgery in patients with UC and CD. We evaluated overall and contemporary risk (after 2000) of surgery and analyzed time trends through mixed-effects meta-regression.

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Results: In patients with UC (26 studies), overall 1-, 5-, and 10-year risk of colectomy was 4.0% (95% CI,3.3–5.0), 8.8% (7.7–10.0) and 13.3% (11.3–15.5), respectively, with decline in risk over time (p<0.001). Corresponding contemporary risks were 2.8% (2.0–3.9), 7.0% (5.7–8.6) and 9.6% (6.3–14.2), respectively. In patients with CD (22 studies), overall 1-, 5-, and 10-year risk of surgery was 18.7% (15.0–23.0), 28.0% (24.0–32.4) and 39.5% (33.3–46.2), respectively, with decline in risk over time (p<0.001). Corresponding contemporary risks were 12.3% (10.8–14.0), 18.0% (15.4–21.0) and 26.2% (23.4–29.4), respectively. On meta-analysis of 8 studies in patients with CD with prior resection, cumulative risk of second resection 5- and 10-years after first resection was 17.7% (13.5–22.9) and 31.3% (24.1–39.6), respectively.

Conclusion: Patient-level risks of surgery have declined significantly over time, with 5-year cumulative risk of surgery of 7.0% in UC, and 18.0% in CD, in contemporary cohorts. This decline may be related early detection and/or better treatment.

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Keywords

Natural history; disease modification; inflammatory bowel diseases; resection; tumor necrosis factor

INTRODUCTION

The global incidence and prevalence of inflammatory bowel disease (IBD) is rising.[1] By 2030, the disease is estimated to affect 1% of individuals in the Western World. IBD is characterized by a lifelong unpredictable relapsing-remitting course, leading to substantial morbidity, diminished quality of life and healthcare resource utilization.[2] Approximately 80% patients require hospitalization, with 25% being readmitted within 30–90 days of admission.[3, 4] A prior meta-analysis suggested that approximately 1/3rd of patients with Crohn's disease (CD) require surgery within 5 years of diagnosis, with the number rising to nearly 50% by 10 years of diagnosis.[5] Similarly, approximately one in six patients with ulcerative colitis (UC) undergo colectomy within 10 years of diagnosis. However, the number of cohorts reporting contemporary surgical risk in patients diagnosed in the 21st century was very small in this meta-analysis. Over the last two decades, several therapeutic measures have improved disease outcomes including: (1) earlier diagnosis, (2) changes in approach to management of IBD with targeted use of disease-modifying immunosuppressive therapy, (3) introduction and increasing uptake of biologic agents like tumor necrosis factor-α antagonists, and (4) earlier detection and endoscopic management of colorectal neoplasia.[6–8] Accordingly, several studies have variably shown a decline in risk of surgery over the last two decades.[9–11]

To better understand surgical risk of IBD in contemporary cohorts, we performed a systematic review with meta-analysis to analyze the cumulative 1-, 5-, and 10-year risk of major abdominal surgery (and repeat surgery in patients with CD) in patients with UC and CD, in population-based inception cohorts.

METHODS

We performed this systematic review based on an *a priori* protocol and reported according to the guidelines as prescribed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[12]

Study Selection

We included population-based cohort studies in patients with incident UC and/or CD, reporting the cumulative risk of major abdominal surgery since time of diagnosis, with at least 1-year minimum follow-up. Population-based studies were identified as those that investigated the entire population in a defined geographical area in a defined time period, used appropriate sampling techniques to infer risk for the entire population, or used national registries capturing nearly the entire population in a region (>90%). For inclusion, these studies were required to report number of patients with incident UC or CD (or number of patients with incident CD with initial abdominal surgery to analyze risk of repeat surgery), calendar year of cohort recruitment, and cumulative risk of surgery estimated by Kaplan-Meier methodology. When multiple studies reported surgical risk from the same cohort, the most comprehensive study reporting from non-overlapping times were included.

We excluded studies that: (1) reported only overall annual surgical rates without patient-level cumulative risk of surgery, (2) reported risk of surgery in patients with IBD, without distinguishing CD or UC, (3) were not population-based (single- or multi-center referral studies, or clinical trials), or (4) reported incidence rate of surgery without cumulative risk.

Search Strategy, Data Extraction and Risk of Bias Assessment

Details of the search strategy, data extraction and risk of bias assessment are reported in the Supplementary Appendix.

Outcomes

The primary outcome was the cumulative 1-, 5- and 10-year risk of major abdominal surgery in patients with UC (defined as colectomy with or without an ileal pouch anal anastomosis) and CD (intestinal resection in patients with CD), and 5- and 10-year risk of repeat major abdominal surgery in patients with CD with initial intestinal resection. While most studies reported cumulative risk at 1-, 5- and 10-year, there were some instances where different cumulative risk at different years were reported. As such, we grouped 1–3y risks as 1-year risk; 4–6y risks as 5-year risk; and 7–10y risk as 10-year risk.

Subsequently, to estimate contemporary risks of surgery in patients diagnosed with IBD in the 21st century, we performed an analysis of cohorts in which the majority of patients were diagnosed after 2000 (>90% cohort).

Statistical Analysis

The pooled risk of major abdominal surgery and 95% confidence intervals (CIs) at 1, 5, and 10 years for both UC and CD, and 5- and 10-year risk of repeat abdominal surgery in patients with CD with prior resection, was estimated using a random effects model.[13]

To estimate 95% CI for individual study estimates from Kaplan-Meier curves, we assumed complete follow-up of the entire cohort. For time-trend analyses, to assess changes in surgical risk over time, the start year of inclusion of patients with incident UC and CD was included as a continuous variable in a meta-regression model of all studies.[5] When the slope of the surgery incidences fit by the mixed-effect model had an associated $p<0.05$, we concluded that the incidence of surgery was changing significantly over time.

Heterogeneity between studies was assessed using the inconsistency index (I^2) with values >50% suggesting significant heterogeneity.[14] We anticipated high statistical heterogeneity as a meta-analysis of cumulative incidence, and took measures to address this in the design stage (strict study inclusion/exclusion criteria) and analysis. We performed subgroup analyses based on geographical location (North America vs. Europe vs. other geographical locations) and age of cohort, with a p-value for differences between subgroups of <0.10 being considered statistically significant. We also conducted mixed effects meta-regression based on population composition (proportion of males) and disease characteristics (UC: proportion of patients with extensive colitis [E3 on Montreal classification]; CD: proportion of patients with ileum-dominant CD [L1/L3 on Montreal classification], proportion of patients with penetrating and/or fibrostenotic behavior [B2/B3 on Montreal classification]); specific data on age at cohort entry was not consistently reported. Sensitivity analyses were performed (1) excluding conference proceedings, and (2) for estimating 10y risk of surgery, by excluding studies in which median population follow-up since diagnosis was <5y or not reported. Publication bias was assessed quantitatively using Egger's regression test (publication bias considered present if $p\leq0.10$), and qualitatively, by visual inspection of funnel plots.[15] All analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 2 (Biostat, Englewood, NJ).

RESULTS

A total 5138 unique studies were identified using our search strategy. Of these, 137 full text articles were reviewed, and 44 studies were included in quantitative synthesis, reporting on 26 cohorts of patients with UC,[11, 16–40] 22 cohorts of patients with CD,[9, 11, 17, 21, 23, 27, 30–32, 39, 41–52] and 8 cohorts of patients with CD with prior surgery.[9, 10, 45, 53–57] Ninety three studies were excluded with detailed reasons reported in eFigure 1.

Cumulative Risk of Colectomy in Patients with Ulcerative Colitis

Table 1 details the characteristics of 26 studies in patients with UC.[11, 16–40] These studies included patients diagnosed between 1962 to 2016, with sample sizes ranging from 41 to 35,782 patients with UC; the largest study was a Danish nationwide register-based study.[11] Six studies reported only on pediatric-onset UC. Fourteen studies reported data from patients in the biologic era, whereas 13 studies reported on surgical risks in the pre-biologic era. Study-level risk-of-bias assessment demonstrated unclear risk of bias, specifically for cohort attrition and reasons for loss to follow-up (Appendix Table 2).

On meta-analysis, the cumulative risk of colectomy 1-, 5-, and 10-years after diagnosis was 4.0% (95% CI, 3.3–5.0), 8.8% (95% CI, 7.7–10.0) and 13.3% (95% CI, 11.3–15.5),

respectively, with considerable heterogeneity (I^2=95–98%) (Figures 1A–C). Time-trend mixed-effects meta-regression showed progressive decline in the 1-, 5- and 10-year risk of colectomy (p<0.01). In contemporary cohorts of patients diagnosed with UC in the 21st century, the cumulative risk of colectomy 1-, 5-, and 10-years after diagnosis was 2.8% (95% CI, 2.0–3.9) [42% lower than in patients diagnosed in prior decades, p=0.01], 7.0% (95% CI, 5.7–8.6) [26% lower than in patients diagnosed in prior decades, p=0.04] and 9.6% (95% CI, 6.3–14.2) [37% lower than in patients diagnosed in prior decades, p=0.04], respectively (eFigures 2A–C).

On subgroup analyses, no significant differences were observed in 1-, 5- and 10-year risk of colectomy based upon geographical location (Appendix Table 3). On meta-regression, study-level sex distribution and disease extent did not affect risk of surgery (Appendix Table 4). Cumulative risk of 1-, 5- and 10-year risk of colectomy in patients with pediatric-onset UC was 5.7% (95% CI, 4.2–7.8), 14.1% (95% CI, 10.0–19.6) and 21.0% (95% CI, 18.8–23.4), respectively. Sensitivity analyses after exclusion of studies published only in abstract form, and cumulative 10y risk of surgery after excluding studies with <5y follow-up, did not significantly change estimates (data not shown).

Cumulative Risk of First Major Abdominal Surgery in Patients with Crohn's Disease

Table 2 details the characteristics of 22 studies in patients with CD reporting on risk of first surgery.[9, 11, 17, 21, 23, 27, 30–32, 39, 41–52] These studies included patients diagnosed between 1955 to 2015, with sample sizes ranging from 53 to 13,185 patients with CD; the largest study was a Danish nationwide register-based study.[11] Two studies were conducted exclusively in pediatric-onset CD. Thirteen studies each reported data from patients in the biologic and pre-biologic era.

On meta-analysis, the cumulative risk of first major abdominal surgery 1-, 5-, and 10-years after diagnosis was 18.7% (15.0–23.0), 28.0% (24.0–32.4) and 39.5% (33.3–46.2), respectively, with considerable heterogeneity (I^2=95–98%) (Figures 2A–C). Time-trend mixed-effects meta-regression showed progressive decline in 1-, 5- and 10-year risk of first major abdominal surgery (p<0.001). In contemporary cohorts of patients diagnosed with CD in the 21st century, cumulative risk of first major abdominal surgery 1-, 5-, and 10-years after diagnosis was 12.3% (10.8–14.0) [48% lower than in patients diagnosed in prior decades, p<0.01], 18.0% (15.4–21.0) [50% lower than in patients diagnosed in prior decades, p<0.01] and 26.2% (23.4–29.4) [44% lower than in patients diagnosed in prior decades, p<0.01], respectively, respectively (eFigures 3A–C).

On subgroup analyses, no significant differences were observed in 1-, 5- and 10-year risk of major abdominal surgery based upon geographical location (Appendix Table 3). On meta-regression, study-level sex distribution, disease extent and behavior did not affect risk of surgery, except a higher 1y risk of surgery in studies with higher proportion of patients with ileum-dominant CD (Appendix Table 4).Cumulative risk of 1-, 5- and 10-year risk of major abdominal surgery in patients with pediatric-onset CD was 8.9% (95% CI, 6.8–11.6), 15.5% (95% CI, 3.0–52.2) and 44.1% (95% CI, 39.9–48.3), respectively. Sensitivity analyses after exclusion of studies published only in abstract form, and cumulative 10y risk

of surgery after excluding studies with <5y follow-up, did not significantly change estimates (data not shown).

Cumulative Risk of Re-Resection in Patients with Crohn's Disease with Prior Surgery

Appendix Table 5 details the characteristics of 8 studies in patients with CD with prior resection. reporting on risk of re-resection.[9, 10, 45, 53–57] These studies included patients diagnosed between 1982 to 2016, with sample sizes ranging from 130 to 8,172 patients with CD with prior resection. Two studies were conducted exclusively in pediatric-onset CD. Three studies each reported data from patients in the biologic and pre-biologic era.

On meta-analysis, the cumulative risk of re-resection 5- and 10-years after first resection was 17.7% (95% CI, 13.5–22.9) and 31.3% (95% CI, 24.1–39.6), respectively, with considerable heterogeneity (I^2=97–98%) (Figures 3A–B). Time-trend mixed-effects meta-regression did not show a significant decline in risk of re-resection (5- and 10-year re-resection, p=0.21 and p=0.16, respectively). In contemporary cohorts of patients diagnosed with CD in the 21st century, the cumulative risk of re-resection in patients with CD with prior resection 5-, and 10-years after diagnosis was 14.8% (95% CI, 11.0–19.7) and 25.5% (95% CI, 11.9–46.6), respectively. Cumulative risk of re-resection in patients with pediatric-onset CD with prior resection 5- and 10-year after diagnosis was 21.4% (95% CI, 14.5–30.4) and 33.6% (95% CI, 27.5–40.2), respectively.

Due to considerable heterogeneity for all analyses, statistical assessment of publication bias was not performed.

DISCUSSION

In this systematic review of 44 population-based cohort studies, we estimated cumulative risk of surgery in patients with UC and CD and observed that short- and long-term risk of surgery was 25–50% lower in patients diagnosed with IBD in the last two decades than prior decades. In contrast to prior estimates, contemporary 5-year risk of major abdominal surgery is 7.0% in UC, and 17.8% in CD, in 21st century. These risks were comparable in patients in North America and Europe, while contemporary data from other parts of the world are evolving. Overall, these findings confirm declining trends in risk of surgery which may be related to disease-modifying effect of contemporary management approach in patients with IBD.

Our systematic review updates a prior comprehensive review on risk of surgery in patients with IBD that was published in 2013.[5] In that review, Frolkis and colleagues included 30 population-based studies in patients with IBD, largely diagnosed before 2007 and followed up to 2011. The number of cohorts reporting contemporary surgical risk in patients diagnosed after 2000 was very small – 3 and 0 cohorts reporting 5- and 10y risk of surgery in UC, and 2 and 0 cohorts reporting 5- and 10y risk of surgery in CD. They inferred progressively lower 5y risk of surgery in patients with CD, but not UC over four decades. The authors speculated that a lower burden of surgery would be observed for patients diagnosed with IBD in the 21st century but could not provide reliable estimates of contemporary surgical risks due to paucity of studies. With an updated literature search,

based on 13 and 12 cohorts of patients with UC and CD, respectively, diagnosed after 2000, we have observed a significantly lower 5- and 10y risks of major abdominal surgery in patients diagnosed at the beginning of the 21st century, than those observed in the 20th century.

Several population-based studies have attempted to examine surgical trends in IBD, over the last decade. However, most studies have examined annual rates of IBD-related surgery amongst patients with prevalent IBD, rather than evaluating individual patient-level cumulative risk of surgery in incident cases. These studies have generally demonstrated decline in annual rates of emergent surgeries in patients with IBD over time. Using administrative claims data from Ontario between 2003–14, Rahman and colleagues observed an approximately 40% decline in resection surgeries in patients with CD between 2003 to 2014, with a corresponding 33% increase in risk of outpatient, non-resection, surgeries for CD (related to perianal fistulae and stricture dilations) over the same time period.[58] Ma and colleagues similarly observed a 3.5% annual decline in rates of surgery in patients with CD between 2002 to 2010, driven primarily by a 10.1% annual decline in rates of emergent surgery, offset by a 3.7% annual increase in rates of elective surgeries.[59] Based upon an administrative claims study, Barnes and colleagues observed similar trends in risk of colectomy in patients with UC.[60] They observed a significant 46% decline in risk of colectomy between 2007 to 2016, with a 4.5-fold increase in use of biologic therapy in the same time period. Kayal and colleagues observed 7.4% annual decline in risk of emergent colectomy in patients with UC, without a significant change in risk of elective ileal pouch anal anastomosis surgeries.[61] While these studies are helpful in informing the overall burden of IBD-related surgeries to the health system, they do not provide patient-level risk estimates that are critical for prognostication for both patient care and development of risk-based treatment algorithms.

The exact factors at play contributing to decrease in risk of surgery in patients with IBD are unclear, though the causes are likely multifactorial and merit further assessment. Whilst reduction in surgical rates has been associated with the parallel increase in use of biologic agents, their exact contribution is hard to quantify. Through claims-based analyses in Ontario, Murthy and colleagues determined that introduction of infliximab may not have resulted in substantial decline in risk of CD- and UC-related surgeries, despite high market penetration in patients with CD.[62] They attributed these findings to “misguided use of infliximab in CD patients and underuse of infliximab in UC”. Other factors such as early diagnosis due to increased patient and provider awareness and improved diagnostics may allow timely introduction of disease-modifying therapy decreasing risk of early surgery. Clinical monitoring and algorithmic treatment escalation have also been shown to decrease the risk of surgery and disease-related complications in the patients with CD.[8, 63] The population-wide, patient-level impact evolving treat-to-target strategies remains to be seen and will be better examined in the coming decade when there is penetration into routine clinical practice. Finally, with better disease control, risk of dysplasia in patients with long-standing UC is decreasing; with advanced endoscopic imaging and therapeutic modalities, several neoplastic lesions, which previously warranted colectomy, are now being managed endoscopically, which is also likely contributing to lower risk of colectomy in patients with UC.[64]

Despite the merits and strengths of our synthesis, there are important limitations. First, considerable heterogeneity was observed in most analyses. However, it is important to note that the implications and interpretation of a statistical measure as I^2 is not the same for studies of incidence and prevalence, as for comparative observational or interventional studies. High statistical heterogeneity is often observed in these analyses and could not be explained despite subgroup and sensitivity analyses, and meta-regression. We tried to minimize conceptual heterogeneity through strict inclusion and exclusion criteria. Other factors including differences in diagnostic evaluation and evolving treatment paradigms and access in different populations may account for unexplained heterogeneity. Second, as noted earlier, we were unable to examine factors that may have contributed to a decline in risk of surgery. There was limited information on use of disease-modifying therapy in these cohorts. Moreover, the potential impact of newer non-TNF-directed biologics, and the practice of cycling through multiple biologics prior to surgery, could not be assessed in these population-based cohorts. Future individual patient-level syntheses are required to comprehensively understand the multitude of factors that may contribute to declining surgical risks. Third, the number of studies examining rates of re-resection in patients with CD was limited, and hence, time-trend analysis was underpowered. Future studies are needed to quantify risk of repeat surgery better. Fourth, studies did not distinguish between types of surgery, including emergent and elective surgeries, resection vs. non-resection surgeries and indications for surgery (for example, medically refractory UC vs. colorectal neoplasia). Risk of surgery for perianal CD was not well-reported. Finally, in pooling cumulative risks, we assumed complete follow-up of cohort which may bias findings particularly for 10y risks of surgery; however, our estimates for long-term risk of surgery were unchanged when limiting to studies with >5y follow-up. Future studies with individual patient-level syntheses of risks, or alternative statistical approaches such as bootstrapping, may provide more reliable estimates.

In conclusion, based on a systematic review of 44 population-based cohorts, we provided robust contemporary cumulative risks of first major abdominal surgery in patients with UC and CD (and repeat surgery in patients with CD) diagnosed in the 21st century. Contemporary cumulative 5-year risk of surgery of 7.0% in UC, and 17.8% in CD is substantially lower than those observed in patients diagnosed in the 20th century. Factors contributing meaningfully to these decreased risks, and cost-effectiveness of those strategies, merit further evaluation, including the impact of newer biologics and treat-to-target strategies, to promote value-based care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures:

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Conflicts of Interest:

- Lester Tsai – None to declare
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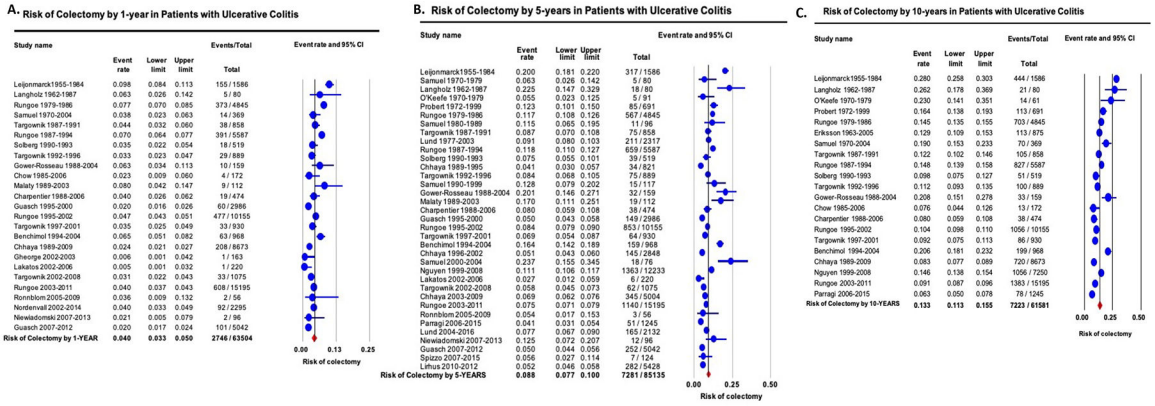

Figure 1.

Cumulative risk of colectomy in patients with ulcerative colitis by (A) 1-year, (B) 5-years and (C) 10-years after diagnosis. Studies are arranged in order of mid-year of cohort recruitment.

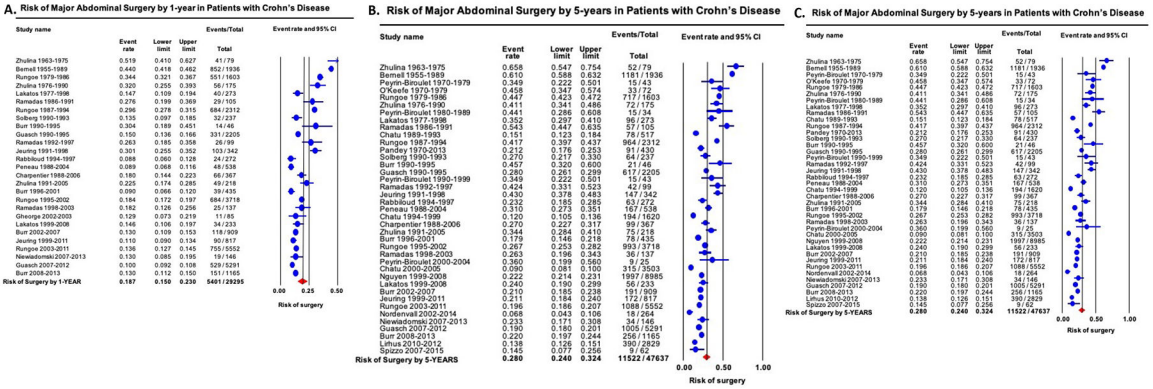

Figure 2.

Cumulative risk of major abdominal surgery in patients with Crohn's disease by (A) 1-year, (B) 5-years and (C) 10-years after diagnosis. Studies are arranged in order of mid-year of cohort recruitment.

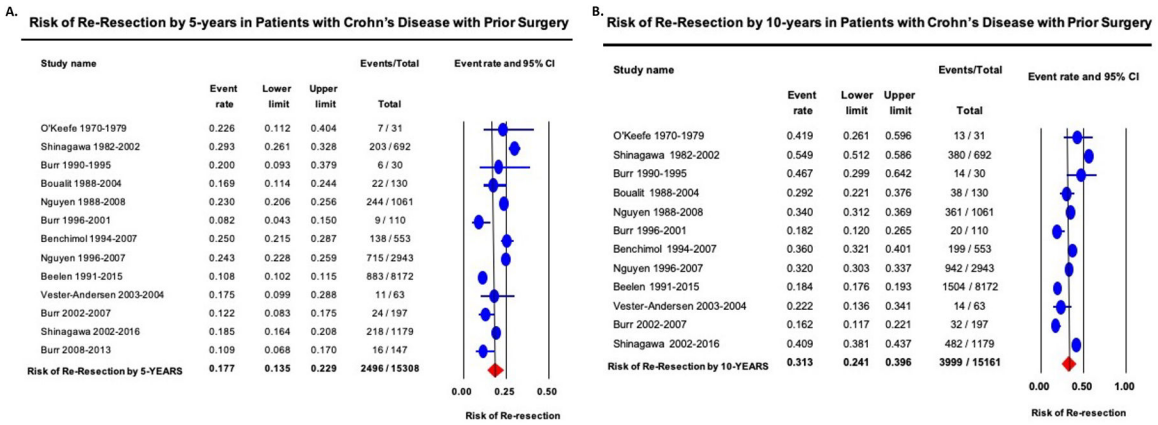

Figure 3.

Cumulative risk of re-resection in patients with Crohn's disease with prior surgery by (A) 5-years and (B) 10-years after first surgery. Studies are arranged in order of mid-year of cohort recruitment.

Table 1.

Characteristics of included studies on colectomy risk in Ulcerative Colitis

Study	Country	Data Source	Study Span (Year)	Sample Size	Age Group	Sex (%)	Extent of Disease (%)	Time Intervals Reported (Years)
Benchimol et al,[16] 2010	Canada	Ontario Province	1994 – 2004	-	Pediatric	-	-	3
Charpentier et al,[17] 2014	France	EPIMAD	1988 – 2006	474	Elderly	M (62), F (38)	E1 (29), E2 (45), E3 (26)	1, 5, and 10
Chhaya et al,[18] 2015	UK	CPRD	1989 – 2009	8673	All ages	M (52), F (48)	-	1, 5, and 10
Chow et al,[19] 2009	China	Prince of Wales Hospital	1985 – 2006	172	All ages	M (52), F (48)	E1 (28), E2 (30), E3 (42)	1 and 10
Eriksson et al,[20] 2017	Sweden	Orebro University Hospital	1963 – 2005	835	All ages	-	-	10
Gheorge et al,[21] 2004	Romania	18 secondary and tertiary centers	2002 – 2003	163	Adults	M (56), F (44)	E1 (22), E2 (54), E3 (24)	1
Gower-Rousseau et al,[22] 2014	France	EPIMAD	1988 – 2004	159	Pediatric	M (42.1), F (57.9)	E1 (25), E2 (38), E3 (37)	1, 5, and 10
Guasch et al,[23] 2018	Spain	ENEIDA	1995 – 2000, 2007 – 2012	8028	All ages	-	-	1 and 5
Lakatos et al,[24] 2011	Hungary	Veszprem Province	2002 – 2006	220	All ages	M (56.8), F (43.2)	E1 (27), E2 (51), E3 (22)	1 and 5
Langholz et al,[25] 1997	Denmark	Copenhagen	1962 – 1987	80	Pediatric	M (53), F (47)	E1 (25), E2 (43), E3 (29)	1, 5 and 10
Leijonmarck et al,[26] 1990	Sweden	Stockholm County	1955 – 1984	1586	All Ages	-	-	1, 5 and 10
Lirhus et al,[27] 2018	Norway	Norwegian Patient Registry	2010 – 2012	5428	All Ages	M (52.8), F (47.2)	-	3
Lund et al,[28] 2019	Denmark	DNPR	1977 – 2016	4449	Pediatric	-	-	5
Malaty et al,[29] 2013	USA	Single Pediatric Center	1989 – 2003	112	Pediatric	M (45), F (55)	E1 (25), E2 (40), E3 (35)	1 and 5
Nguyen et al,[30] 2017	Canada	Ontario Province	1999 – 2008	12233	Adult	M (48.7), F (51.3)	-	5 and 10
Niewiadomski et al,[31] 2015	Australia	Barwon Area	2007 – 2008, 2010 – 2013	96	All ages	-	-	1 and 5
Nordenvall et al,[32] 2018	Sweden	Swedish Patient Register	2002 – 2014	2295	Pediatric	M (54), F (46)	-	3
O'Keefe et al,[33] 1989[a]	South Africa	Cape Town	1970 – 1979	91 (5y), 61 (10y)	All ages	-	-	5 and 10

Study	Country	Data Source	Study Span (Year)	Sample Size	Age Group	Sex (%)	Extent of Disease (%)	Time Intervals Reported (Years)
Parragi et al,[34] 2018	Switzerland	SIBDCS	2006 – 2015	1245	All ages	M (54.6), F (45.4)	E1 (20), E2 (32), E3 (38)	5 and 10
Probert et al,[35] 1993	England	Leicestershire	1972 – 1989	691	All ages	-	-	5 and 10
Ronnblom et al,[36] 2016	Sweden	Uppsala Healthcare Region	2005 – 2009	524	All ages	M (55.2), F (44.8)	E1 (32), E2 (31), E3 (31)	1 and 5
Rungoe et al,[11] 2014	Denmark	DNPR	1979 – 2011	35782	All ages	M (47), F (53)	-	1, 5, and 9
Samuel et al,[37] 2013	USA	Olmsted County	1970 – 2004	369	All ages	M (58), F (42)	E1 (29), E2 (37), E3 (32)	1, 5, and 10
Solberg et al,[38] 2009	Norway	IBSEN	1990 – 1993	519	All ages	M (51.4), F (48.6)	E1 (33), E2 (35), E3 (32)	1, 5, and 10
Spizzo et al,[39] 2016	Australia	GECCO	2007 – 2015	41	All ages	-	-	4
Targowinik et al,[40] 2012	Canada	UMIBDED	1984 – 2008	3752	All Ages	M (48), F (52)	-	1, 5, and 10

M: Male, F: Female, E1: Proctitis, E2: Left-sided Colitis, E3: Pancolitis

Table 2.

Characteristics of included studies on primary resection risk in Crohn's Disease

Study	Country	Data Source	Study Span (Year)	Sample Size	Age Group	Sex (%)	Location at Diagnosis (%)	Behavior at Diagnosis (%)	Time Intervals Reported (Years)
Bernell et al,[41] 2000	Sweden	Stockholm County	1955 – 1989	1936	All ages	M (47) F (53)	-	-	1, 5, and 10
Burr et al,[9] 2019	UK	Research One	1994 – 2013	3059	All ages	M (47) F (53)	-	-	1, 5, and 10
Charpentier et al,[17] 2014	France	EPIMAD	1988 – 2006	367	Elderly	M (38) F (62)	-	B1 (78), B2 (17), B3 (5)	1, 5, and 10
Chatu et al,[42] 2014	UK	CPRD	1989 – 2010	5640	All ages	M (42) F (57)	-	-	5
Gheorge et al,[21] 2004	Romania	18 secondary and tertiary centers	2002 – 2003	85	Adults	M (57) F (43)	L1 (15), L2 (52), L3 (32), L4 (2)	-	1
Guasch et al,[23] 2018	Spain	ENEIDA	1990 – 1995, 2007 – 2012	7496	All ages	-	-	-	1 and 5
Jeuring et al,[43] 2015	Netherlands	IBD-SL	1991 – 2011	1159	All ages	-	-	-	1, 5, and 10
Lakatos et al,[44] 2012	Hungary	Veszprem Province	1977 – 2008	506	All ages	M (49.6) F (50.4)	L1 (32.8), L2 (36.0), L3 (30.6), L4 (0.6)	B1 (56.9), B2 (19.8), B3 (23.3)	1, 5, and 10
Lirhus et al,[27] 2018	Norway	Norwegian Patient Registry	2010 – 2012	2829	All Ages	M (47.5) F (52.5)	-	-	3
Nguyen et al,[30] 2017	Canada	Ontario Province	1999 – 2008	8985	Adult	M (44.3) F (55.7)	-	-	5 and 10
Niewiadomski et al,[31] 2015	Australia	Barwon Area	2007 – 2008, 2010 – 2013	146	All ages	-	-	-	1 and 5
Nordenvall et al,[32] 2018	Sweden	Swedish Patient Register	2002 – 2014	2174	Pediatric	M (58) F (42)	-	-	3
O'Keefe et al,[45] 1989 [b]	South Africa	Cape Town	1970 – 1979	72 (5y), 53 (10y)	All ages	-	-	-	5 and 10
Pandey et al,[46] 2015	Singapore	8 hospitals	1970 – 2013	430	All ages	M (61.8) F (38.2)	L1 (27.7), L2 (27.7), L3 (41.9), L4 (17.9)	B1 (78.1), B2 (14.0), B3 (7.9)	5 and 10
Peneau et al,[47] 2012	France	EPIMAD	1988 – 2004	538	Pediatric	-	-	-	1, 5, and 10
Peyrin-Biroulet et al,[48] 2012	USA	Olmsted County	1970 – 2004	310	All ages	M (50.3) F (49.7)	L1 (31.2), L2 (33.1), L3 (33.4), L4 (2.3)	B1 (81.3), B2 (4.6), B3 (14.1)	5 and 10
Rabilloud et al,[49] 2016	France	Brittany Area	1994–1997	272	All ages	-	-	-	1, 5, and 10

Study	Country	Data Source	Study Span (Year)	Sample Size	Age Group	Sex (%)	Location at Diagnosis (%)	Behavior at Diagnosis (%)	Time Intervals Reported (Years)
Ramadas et al,[50] 2010	UK	Cardiff	1986 – 2003	341	All ages	M (38) F (62)	-	-	1 and 5
Rungoe et al,[11] 2014	Denmark	DNPR	1979 – 2011	13185	Adult	M (41) F (59)	-	-	1, 5, and 9
Solberg et al,[51] 2007	Norway	IBSEN	1990 – 1993	237	All ages	M (50.2) F (49.8)	L1 (27), L2 (48.5), L3 (22.8), L4 (1.7)	B1 (62.0), B2 (27.0), B3 (11.0)	1, 5, and 10
Spizzo et al,[39] 2016	Australia	GECCO	2007 – 2015	62	All ages	-	-	-	4
Zhulina et al,[52] 2016	Sweden	Orebro University Hospital	1963 – 2005	472	All ages	M (47) F (53)	L1 (40.5), L2 (33.9), L3 (23.7), L4 (1.7)	B1 (63.5), B2 (19.5), B3 (16.7)	1 and 5

M: Male, F: Female, L1: Ileal, L2: Colonic, L3: Ileocolonic, L4: Upper GI Tract, B1: Inflammatory, B2: Fibrostenotic, B3: Penetrating