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Decreasing Trends in Intestinal Resection and Re-Resection in Crohn's Disease

A Nationwide Cohort Study

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Objective: To assess time trends in intestinal resection and re-resection in Crohn's disease (CD) patients.

Summary of Background Data: CD treatment has changed considerably over the past decades. The effect of these advances on the necessity of intestinal resections and the risk of re-resection is unclear.

Methods: In this nationwide cohort study, adult CD patients with ileocolonic, small bowel, colon, or rectum resections between 1991 and 2015 were included. Data were retrieved from the Dutch nationwide network and registry of histopathology and cytopathology (PALGA). Time trends were analyzed with a broken stick model and Cox proportional hazard model with smoothing splines.

Results: The identified cohort comprised 8172 CD patients (3293/4879 male/female) in whom 10,315 intestinal resections were performed. The annual intestinal resection rate decreased nonlinearly from 22.7/100,000 CD patients (1991) to 2.5/100,000 (2015). A significantly steeper decrease was observed before 1999 (slope −1.56) as compared to subsequent years (slope −0.41) ($P < 0.001$). Analogous trends were observed for ileocolonic, small bowel, and colon resections. Overall cumulative risk of re-resection was 10.9% at 5 years, 18.6% at 10 years, and 28.3% at 20 years after intestinal resection. The hazard for intestinal re-resection showed a nonlinear decreasing trend, with hazard ratio 0.39 (95% confidence interval 0.36–0.44) in 2000 and hazard ratio 0.25 (95% confidence interval 0.18–0.34) in 2015 as compared to 1991.

Conclusion: Over the past 25 years, intestinal resection rate has decreased significantly for ileocolonic, small bowel, and colonic CD. In addition, current postoperative CD patients are at 75% lower risk of intestinal re-resection.

Keywords: ileocecal resection, inflammatory bowel disease, surgery, time trends

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BACKGROUND

Crohn's disease (CD) patients are at a high risk of intestinal resection. According to the available studies, the cumulative risk of intestinal surgery in CD is 50% after a disease duration of 10 years.[1] The need for intestinal resection in CD may be decreasing, as CD management has changed significantly over the past decades.[2–4] First, treatment goals have shifted from primarily symptom control to mucosal healing, which is associated with a better CD prognosis, characterized by long-term clinical and endoscopic remission as well as increased quality of life.[5,6] Second, widespread availability and early use of immunomodulatory and biological agents have changed treatment algorithms. The exposure to immunosuppressants as well as anti-tumor necrosis factor (TNF) has increased significantly over the past decades.[7] Third, strict monitoring to achieve the treatment goals has been introduced, with lower thresholds for endoscopy or radiologic imaging, and this strategy has made important leaps forward by implementation of noninvasive fecal calprotectin tests and therapeutic drug monitoring.[8] In addition to these changes in general CD management, the need for re-resection after first intestinal resection may be reduced after large trials have advocated specific strategies to prevent postoperative CD recurrence[9–11] and international guidelines focusing on the management of CD to prevent postoperative recurrence were deployed.[12,13]

The impact of these changed treatment paradigms on the frequency of intestinal surgery in CD and the risk of re-resection is uncertain. Available studies have shown conflicting results and have reported decreasing trends[14–16] as well as stable rates.[17–19] Important shortcomings of available data are the lack of details on the anatomic location of intestinal resection, and the relatively small size of the cohorts. Moreover, data from most recent years are required, as

CD treatment strategies are continuously evolving. Data on the rate of necessity of re-resection would be highly valuable, as a decrease in surgical recurrence is a robust indicator of improved postoperative prognosis. In this study, we aimed to assess recent time trends in rates of intestinal resection as well as re-resection for CD in a nationwide cohort study in the Netherlands.

METHODS

Data Collection

All histopathology and cytopathology reports in the Netherlands are stored in the Dutch nationwide population-based pathology database (PALGA). Patients are pseudonymized with a unique code and all consecutive pathology reports are combined with standardized diagnostic codes to allow for anonymized follow-up per patient. Since 1991, this database has nationwide coverage.[20] Follow-up data were evaluated until December 2015.

All patients aged ≥18 years with a histological diagnosis of CD, as coded by a pathologist, and an intestinal resection between 1991 and 2015 were identified in the PALGA database. All ileocolonic resections, small bowel resections, colon resections, and rectum resections were identified from the database using specific diagnostic coding, registered by the pathologist when writing the pathology report (Appendix, Supplemental Digital Content 1, http://links.lww.com/SLA/B676). Intestinal resections for malignancy were excluded through specific coding and hand-searching. Afterwards, duplicate (revision material) reports were excluded. For each patient, the following characteristics were available: sex, date of birth, date of pathology report, summary of pathology text, and diagnostic code. The date of death is not provided in PALGA, unless an autopsy had been performed. Therefore, censoring for death was derived from survival data from Statistics Netherlands (CBS).[21] For each patient, the imputed total follow-up time was based on life expectancy in the year of birth, assuming the survival of CD patients is similar to the general population.[22,23]

Statistical Analysis

Statistical analyses were performed with IBM SPS Statistics version 22.0 (IBM Corp. Released 2013; IBM Corp, Armonk, NY) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) with the packages survival and splines.[24,25] Continuous data are presented as median and interquartile range (IQR). CD prevalence rates between 1991 and 2015 were estimated using prevalence in 2010, yearly CD incidence rates as reported by a recent population-based cohort study,[23] and the life expectancy given the patient's year of birth, under the assumption life expectancy in CD patients is similar to the general population.[22,23] Total population numbers and mortality rates in the Netherlands were available via Statistics Netherlands (CBS).[26] To investigate whether the assumed similar life expectancy of CD patients as compared to the general population has affected our results, a sensitivity analysis was performed using an elevated standardized mortality ratio of 1.38 in CD patients, as described by Bewtra et al.[27]

Time Trends in Intestinal Resections

The annual number of resections per 5-year interval and corresponding patient characteristics were described and compared across intervals. Medians were compared using Mann-Whitney *U* tests.

Time trends in the number of intestinal resections corrected for CD prevalence (number of resections per 100,000 CD cases) were explored and modeled using linear regression with natural cubic splines (for all types of resection and per anatomic location). Visual inspection indicated that the curve could be sufficiently approximated by a piecewise linear model,[28] which facilitates a more straightforward interpretation. The piecewise linear model used 1 breakpoint and allowed different linear fits on either side. The position of the breakpoint was chosen to optimize the Bayesian information criterion (BIC) and the BIC of the simplified model compared to that of the original model to confirm that the approximation was appropriate.

Intestinal Re-Resection

The cumulative incidence of re-resection (for all types of resections and per anatomic location), was assessed using Kaplan-Meier survival analysis and compared using log-rank test. Cox-regression analysis was performed to evaluate the association of re-resection with sex, age at first resection, year of first resection, and anatomic location of first resection. To investigate the shape of this association, in a second step, the effects of continuous covariates (age and year of first resection) were modeled using penalized splines (p-splines), which allow deviation from the standard assumption of linear effects. Nonlinearity was tested using Chi-squared goodness-of-fit tests.[29]

RESULTS

Study Population

The identified cohort comprised 8172 CD patients [male 3293 (40%); female 4879 (60%)], with a median age of 38.0 years (IQR 27.0 to 51.0) at (first) intestinal resection, in whom 10,315 intestinal resections were performed between 1991 and 2015. According to anatomic location, the first identified intestinal resection was an ileocolonic resection in 3186/8172 patients (39%), small bowel resection in 2551 (31%), colon resection in 2262 (28%), and rectum resection in 173 (2%; Table 1).

Time Trends in Intestinal Resections

An increase in the mean absolute annual number of intestinal resections was observed during the study period, for all specific anatomic locations. Patients underwent intestinal resection at a significant younger median age during the period 1991 to 1995 [35.0 years (IQR 27.0 to 49.0)] and the period 1996 to 2000 [37.0 years (IQR 28.0 to 50.0)], as compared with subsequent time periods, $P < 0.001$. No further significant increase in age at resection was observed after the year 2000 (Supplementary table, Supplemental Digital Content 2, http://links.lww.com/SLA/B676).

The total intestinal resection rate decreased nonlinearly during the study period from 22.7/100,000 CD patients in 1991 to 2.5/100,000 in 2015 (Fig. 1A). The piecewise linear model used a breakpoint in 1999 with a slope of −1.56 [95% confidence interval (95% CI) −1.75 to −1.36] per year before 1999 and −0.41 (95% CI −0.49 to −0.33) per year after 1999 (both $P < 0.001$; Fig. 1B).

Similar nonlinear decreasing trends were observed for all subgroups of intestinal resection. The overall decrease was most substantial for ileocolonic resections, from 7.9/100,000 in 1991 to 1.3/100,000 in 2015. Colon and small bowel resections decreased from 6.7/100,000 in 1991 to 0.6/100,000 in 2015 and 6.8/100,000 in 1991 to 0.8/100,000 in 2015, respectively (Fig. 2). Rectum resection rates decreased from 0.5/100,000 in 1991 to 0.01/100,000 in 2015. Piecewise linear models used the year 2000 as the breakpoint for ileocolonic resections and small bowel resections, with corresponding slopes before and after 2000 of −0.55 (95% CI −0.65 to −0.46) and −0.12 (95% CI −0.17 to −0.07), respectively, for ileocolonic and −0.41 (95% CI −0.48 to −0.34) and −0.15 (95% CI −0.19 to −0.11) for small bowel resections (all $P < 0.001$). The year 1998 was found to be the breakpoint for colon resections, with a slope of −0.52 (95% CI −0.62 to −0.42) before 1998 and −0.11 (95% CI −0.14 to

TABLE 1. Patient Characteristics

			Total (N = 8172)
Male sex		N (%)	3293 (40)
Age at intestinal resection, y		Median (IQR)	38.0 (27.0–51.0)
Number of intestinal resections	1		6658 (81)
	2	N (%)	1160 (14)
	>2		354 (5)
Anatomic location first intestinal resection	Ileocolonic		3186 (39)
	Small bowel	N (%)	2551 (31)
	Colon		2262 (28)
	Rectum		173 (2)

IQR indicates interquartile range.

−0.08) after 1998. Rectum resection models showed a linear decrease without the need for a breakpoint. Here, the slope was −0.02 [95% CI (−0.03 to −0.02)] (Supplementary figure, Supplemental Digital Content 3, http://links.lww.com/SLA/B676). All piecewise linear models approximated the smooth fit sufficiently well (difference in BIC < 5).

Intestinal Re-Resection

During a median follow-up of 9.4 years (IQR 4.4 to 15.3) after first resection, intestinal re-resection was performed in 1547/8172 (19%) patients and more than 2 intestinal resections were performed in 354/8172 (5%) patients. The re-resection concerned a small bowel resection in 563/1547 (36%) patients, ileocolonic resection in 482 (31%) patients, colon resection in 391 (26%) patients, and rectum resection in 111 (7%) patients (Supplementary table, Supplemental Digital Content 4, http://links.lww.com/SLA/B676).

The cumulative incidence of intestinal re-resection in the total cohort was 10.8%, 5 years after the first resection, and increased to 18.4%, 23.9%, and 28.2% after 10, 15, and 20 years of follow-up, respectively (Fig. 3A). The cumulative incidence of intestinal re-resection after isolated colon resection was 15.4% at 5 years, 21.5% at 10 years, 24.7% at 15 years, and 26.9% at 20 years after first intestinal resection. Intestinal re-resection rates for small bowel resection were 10.5%, 19.0%, 25.0%, and 29.3% and for ileocolonic resection 8.0%, 16.2%, 23.1%, and 28.7%, after 5, 10, 15, and 20 years. Intestinal re-resection rates after rectum resection were lower, 6.9% at 5 years increasing to 10.3%, 11.2%, and 14.4% at 10, 15, and 20 years, respectively (log-rank $P < 0.001$; Fig. 3B).

The risk of intestinal re-resection per anatomic location of first resection and re-resection is shown in Fig. 4A to C. After ileocolonic resection, the cumulative risk of re-resection after 10 years was 6.7% for ileocolonic anastomosis, 6.4% for small bowel, and 3.3% for colon. After small bowel resection, the risk of re-resection after 10 years was 10.5% for small bowel, 6.1% for ileocolon, and 3.1% for colon. After a colonic resection, the risk of a re-resection after 10 years was 10.6% for colon, 3.8% for ileocolon, and 5.6% for small bowel.

In multivariable Cox regression analysis, colon resections and small bowel resections had significantly higher hazards of re-resection as compared to ileocolonic resections, hazard ratio (HR) 1.38 (95% CI 1.21–1.56) $P < 0.001$ and HR 1.17 (95% CI 1.03–1.32) $P = 0.015$. Patients who had had a rectum resection had a lower hazard as compared to patients with ileocolonic resections, HR 0.61 (95% CI 0.39–0.96) $P = 0.032$. Older age at the moment of first resection was a significant protective factor for postoperative intestinal re-resection in multivariable analysis, HR 0.99 per year (95% CI 0.98–0.99) $P < 0.001$. Finally, patients undergoing the first resection during a later calendar year of follow-up were at a significantly lower hazard of re-resection, HR 0.94 per year (95% CI 0.93–0.95) $P < 0.001$, indicating a decreasing time trend in intestinal re-resection between 1991 and 2015. There was no evidence for an effect of sex (Supplementary table, Supplemental Digital Content 5, http://links.lww.com/SLA/B676).

FIGURE 1. Intestinal resection rate in CD patients between 1991 and 2015 (A) its corresponding piecewise linear model (B) and corresponding 95% confidence intervals. Prevalence of Crohn's disease: prevalence per 100,000 persons.

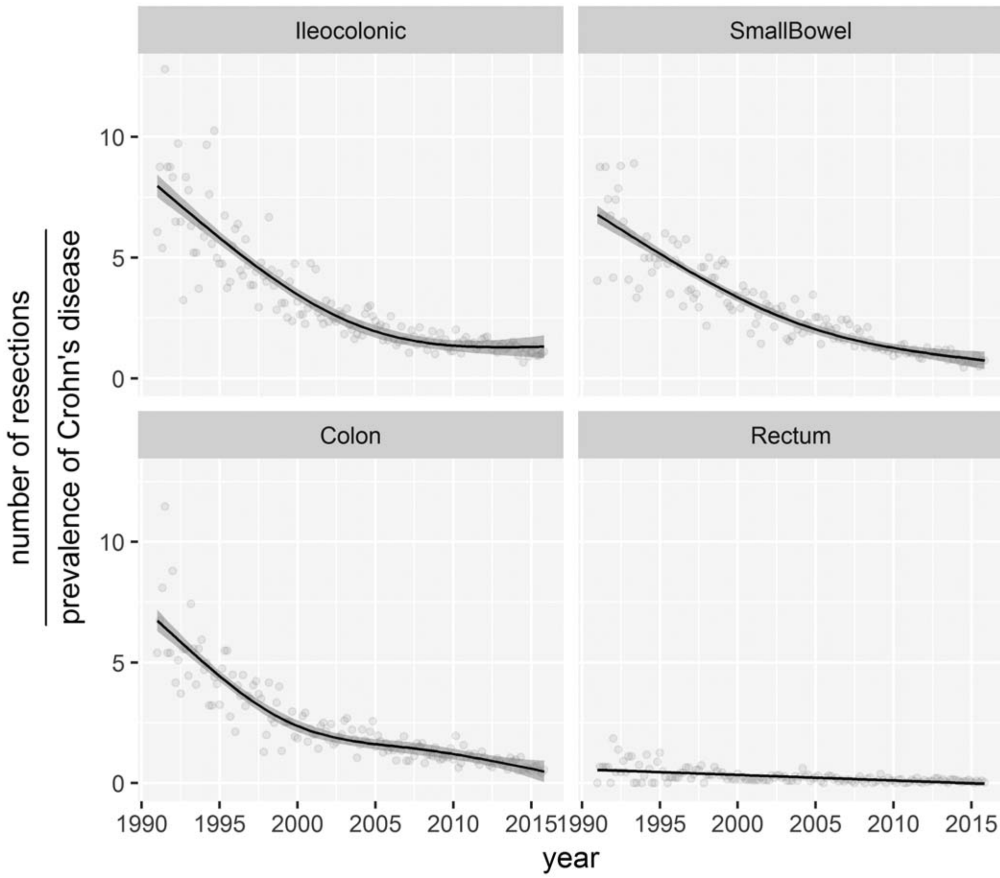
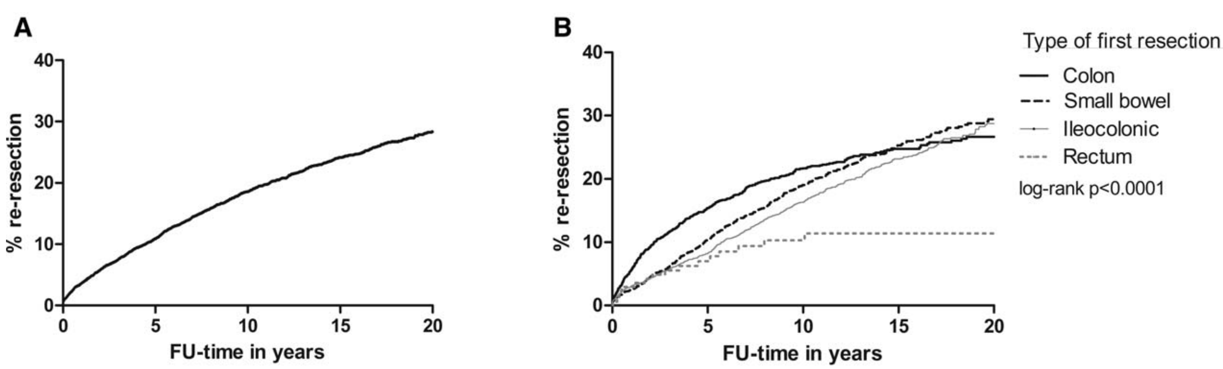


FIGURE 2. Intestinal resection rate in CD patients according to anatomic location: Ileocolonic, colon, small bowel, and rectum and corresponding 95% confidence interval. Prevalence of Crohn's disease: prevalence per 100,000 persons.

Chi-squared tests for goodness-of-fit showed the effect of year of first resection was nonlinear. There was no evidence of a nonlinear effect of age at first resection. Visualization of the multivariable Cox model showed the steepest decline in HR for re-resection was observed during the first years of inclusion (Fig. 5). As compared to 1991, corresponding HRs decreased to 0.43 in 2000 (95% CI approx. 0.38–0.48 for ileocolon, small bowel, and colon; 95% CI 0.27–0.67 for rectum), and 0.28 in 2015 (95% CI approx. 0.21–0.36 for ileocolon, small bowel, and colon; 95% CI 0.17–0.46 for rectum).

Sensitivity analyses under the assumption of an elevated standardized mortality ratio of 1.38 did not show any significant differences in intestinal resection and re-resection rates.



Patients at risk	0 years	5 years	10 years	15 years	20 years
Total	8172	5594	3535	1844	643

Patients at risk	0 years	5 years	10 years	15 years	20 years
Colon	2184	1455	902	450	162
Small bowel	2523	1826	1133	579	197
Ileocolonic	3186	2193	1417	769	266
Rectum	279	121	86	49	23

FIGURE 3. Cumulative risk of intestinal re-resection during follow-up for the total study population (A) and according to anatomic location of first resection (B). FU indicates follow-up.

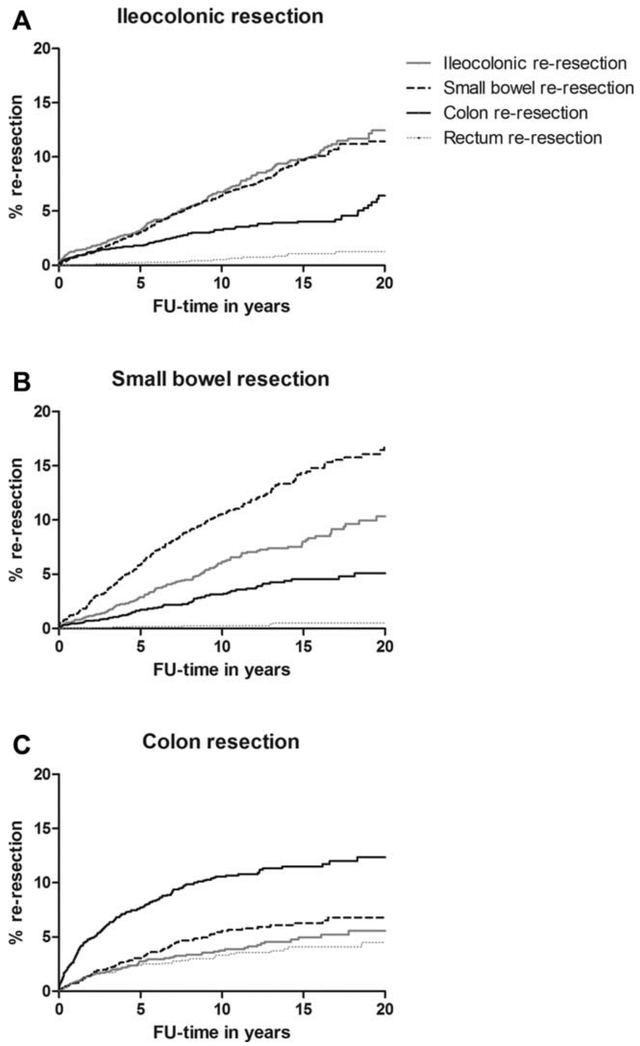


FIGURE 4. . Cumulative risk of intestinal re-resection according to anatomic location of initial resection: ileocolonic (A), small bowel (B), and colon (C). FU indicates follow-up.

DISCUSSION

The risk of intestinal resection in CD patients has decreased significantly over the past 25 years according to the long-term follow-up data in this nationwide cohort. A substantial decrease of intestinal resections in CD patients over the past decades was observed for all anatomic locations. Furthermore, a decreasing trend in the risk of intestinal re-resection was observed, with a 4 times lower hazard in 2015 as compared to 1991.

Epidemiological trends on the intestinal resection rate in CD patients have been investigated widely, as intestinal resection can be regarded as a surrogate marker of CD course and prognosis. However, previous studies have shown inconsistent results, and both decreasing and stable trends have been reported. These inconsistencies may be explained by inclusion of a relatively small number of patients (ie, less than 500), hampering reliable assessment of epidemiological trends.[15,16,18,19,30] In contrast to our observations, a stable annual intestinal resection rate of 3.4/100,000 persons was observed in a large cohort of 359,124 hospitalized CD patients from the US Nationwide Inpatient Sample (NIS).[17] The intestinal resection rate is lower in these USA data as compared to our cohort, which can probably be explained by not correcting for the substantial rise in CD prevalence and the relatively short study period. In line with our results, a large study of 4146 CD patients who underwent an intestinal resection reported a significant decrease in risk of surgery in 4 pre-defined cohorts according to year of diagnosis, between 1979 and 2011. This observation was associated with a significant increase in use of thiopurines and anti-TNFα.[31]

Although we observed a continuing decrease of intestinal resections after 2000, the most substantial decreasing trend in intestinal resection and in intestinal re-resection was observed between 1991 and 1999. Important changes in CD diagnosis as well as management may account for these observations. Over the past decades, earlier disease detection has contributed to a less complicated disease phenotype at diagnosis over the past decades.[7] A lower risk of resection shortly after diagnosis due to less severe complications at diagnosis is probably an important explanation for the observed decline in intestinal resections, especially for the period before 1999. In addition, the decline in intestinal resections is paralleled by significant changes in drug therapy, most importantly the introduction of thiopurines and anti-TNFα.[32–35] A changing phenotype attributable to widespread use of immunomodulators and anti-TNFα, with less progression toward stricturing and penetrating disease complications, may have contributed to the observed decline in intestinal resections, before 1999 as well as the continuing decline after 2000. However, whether drug therapy changes the natural course of CD is still a matter of debate.[7,30] Instead or in addition to changing the course of disease, the introduction of more therapeutic options in CD may be a contributing factor to postponement of intestinal resection, a hypothesis that is supported by our observation of a significant younger median age at resection between 1991 and 1999, as compared to time periods after 2000.

Other factors that may be involved in the decline of intestinal resections are strict monitoring of inflammation with broader access to endoscopy, including video capsule endoscopy (VCE), and validation of (new) radiologic tools, for example, computed tomography (CT) and magnetic resonance imaging (MRI).[36,37] In addition, noninvasive monitoring with fecal calprotectin has been implemented widely in clinical practice.[8] Furthermore, a decrease in the number of active smokers may have contributed to the decline in intestinal resections and re-resections.[30]

In this study, we focused on intestinal resections for nonmalignancy indications in CD, and resections with neoplasia were excluded from analysis. It may be hypothesized that the observed decrease in nonmalignancy indications may induce a shift in indications from refractory CD and CD complications (eg, stenosis, penetrating disease) toward neoplasia, especially when surgery is postponed. However, this hypothesis is not substantiated by our data. Before exclusion from the main analysis, 266 resections (87% colon) with neoplasia (178 carcinoma and 97 dysplasia) were identified during 25 years study period. Although these low numbers do not allow for time trend analysis, these data indicate that neoplasia represent only a small proportion of the indications for intestinal resection in CD. With regard to the absolute risk of neoplasia in CD, this finding needs to be interpreted cautiously as the number of intestinal neoplasia may be underestimated, due to the possibility of endoscopic resection of colonic neoplasia and coding IBD instead of CD in the PALGA database.

We observed a marked decreasing trend in intestinal re-resection risk during the entire study period from 1991 to 2015. This finding may probably be due to improved and continuously evolving postoperative CD management. The risk of re-resection in our cohort is lower as compared to the results of a meta-analysis of 6 population-based studies with data inclusion from time periods

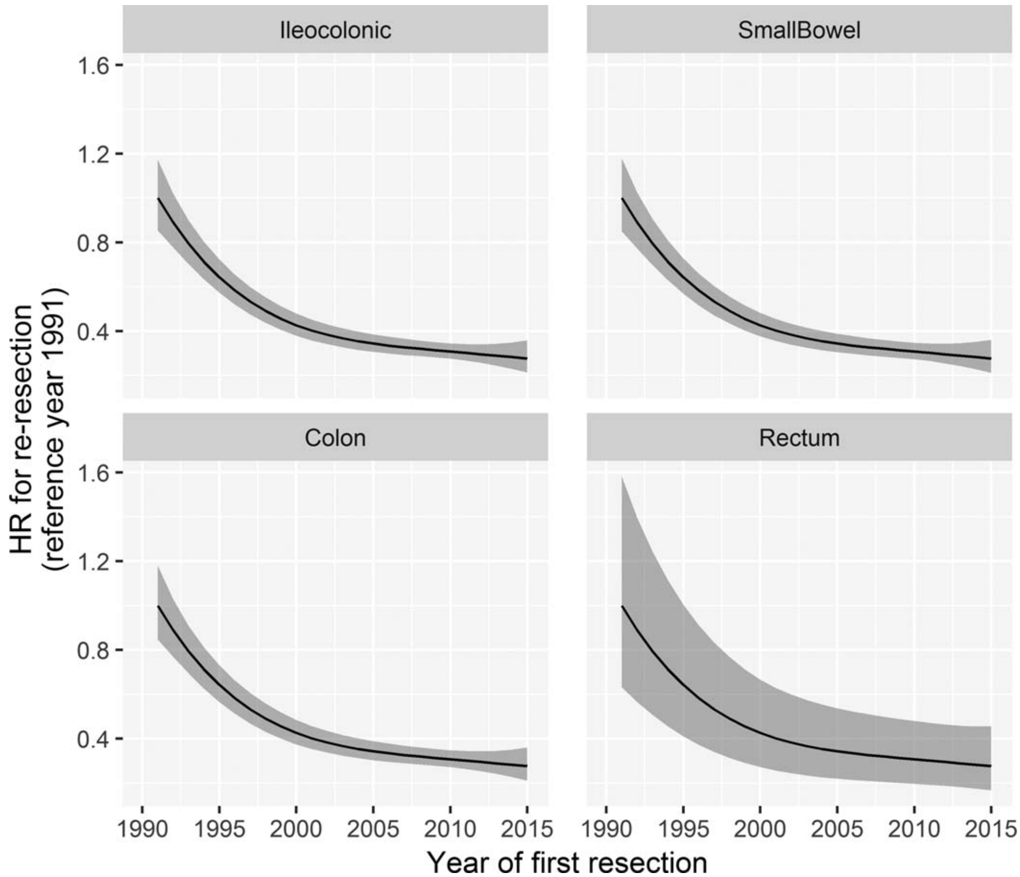


FIGURE 5. Hazard ratio for intestinal re-resection over the past 25 years (reference year 1991) and corresponding 95% confidence interval. Age and sex are set to reference values (median age = 37; sex = male). Prevalence of Crohn's disease: prevalence per 100,000 persons. HR indicates hazard ratio.

varying from 1970 to 1979 to 1996 to 2007, which reported a re-resection risk of 24.2% after 5 years, and 35.0% after 10 years.[38] This difference can partly be explained by the inclusion of older and smaller cohorts in the meta-analysis.

The anatomic location of resection and subsequent re-resection was the same in the majority of patients in our study, most notably after a first colon or small bowel resection. This implies the CD location in the bowel is rather stable during the disease course, which is supported by evidence of a relatively stable Vienna classification in terms of disease localization.[39] Patients with a first colon resection were at highest hazard of intestinal re-resection, and the most frequently performed type of re-resection was a repeated colonic resection. Our data are in line with a previously reported high risk of re-resection after a segmental colon resection.[40–42] However, as segmental colonic resections have apparent advantages, for example, a reduced risk of permanent stoma and a better reported quality of life,[43,44] a debate on the surgical management of Crohn's colitis is ongoing.

To the best of our knowledge, this is the largest study reporting time trends in intestinal resection and re-resections in CD. This study substantially adds to available literature by showing more recent trends and yearly resection rates for the specific anatomic locations, in a CD population with nationwide coverage and an assured detection of all intestinal resections and follow-up per patient. Despite these strengths, a few limitations need to be considered. First, we regarded the first available surgical excerpt in our database as the first resection. In a small number of patients, this might be a re-resection, if the first resection was performed before 1991. This might have led to an underestimation of the re-resection risk in our results. Second, a relatively high proportion of patients with small bowel resections was included. We assume that ileocecal resections may be coded as small bowel resections in a proportion of patients. However, as coding has not changed during the study period, we anticipate that this misclassification is stable over time and has not influenced the evaluation of time trends. As mentioned above, the possibility of coding IBD instead of CD in the PALGA database may have led to an underestimation of the total number of intestinal resections. Nevertheless, time trend analysis of large number of resections during long-term follow-up will not be affected by accidental miscoding. Third, resections might have been performed for an indication other than CD, such as diverticulitis in a CD patient. However, as the number of cases is probably very limited and resections for malignancy were excluded, the effect on the results is presumably negligible. Finally, the most important limitation of this study is the lack of data on other associated factors for intestinal resection in CD, such as disease duration, smoking status, disease behavior, CD medication use, length of the resected segment, and surgical techniques. These additional data would enable interpretation of the contributing factors of the decline in surgery rate in times of rapidly changing CD management strategies.

In conclusion, our study demonstrated a substantial decrease in ileocolonic, small bowel, and colon resections in CD patients over the past 25 years, with the most significant decrease before 1999. The risk of intestinal re-resection has shown a striking decline over the past decades, and current risk is approximately 4 times lower as compared to 1991.

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