Risk of Surgery for Inflammatory Bowel Diseases Has Decreased Over Time: A Systematic Review and Meta-analysis of Population-Based Studies

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This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of the CME activity, successful learners will be able to summarize trends in surgery risk over time in IBD patients.

BACKGROUND & AIMS: The inflammatory bowel diseases (IBDs) are chronic diseases that often require surgery. However, the risk of requirement of surgery over time has not been well characterized. We performed a systematic review and meta-analysis to establish the cumulative risk of surgery among patients with IBD and evaluated how this risk has changed over time. **METHODS:** We searched Medline, EMBASE, PubMed, and conference proceedings (2009–2012) on May 8, 2013, for terms related to IBD and intestinal surgery. Two reviewers screened 8338 unique citations to identify 486 for full-text review. The analysis included population-based studies published as articles (n = 26) and abstracts (n = 4) that reported risks of surgery at 1, 5, or 10 years after a diagnosis of Crohn's disease and/or ulcerative colitis. The trend in risk of surgery over time was analyzed by meta-regression using mixed-effect models. **RESULTS:** Based on all population-based studies, the risk of surgery 1, 5, and 10 years after diagnosis of Crohn's disease was 16.3% (95% confidence interval [CI], 11.4%–23.2%), 33.3% (95% CI, 26.3%–42.1%), and 46.6% (95% CI, 37.7%–57.7%), respectively. The risk of surgery 1, 5, and 10 years after diagnosis of ulcerative colitis was 4.9% (95% CI, 3.8%–6.3%), 11.6% (95% CI, 9.3%–14.4%), and 15.6% (95% CI, 12.5%–19.6%), respectively. The risk of surgery 1, 5, and 10 years after diagnosis of Crohn's disease and 1 and 10 years after diagnosis of ulcerative colitis has decreased significantly over the past 6 decades ($P < .05$). **CONCLUSIONS: Based on systematic review and meta-analysis of population-based studies, the risk of intestinal surgery among patients with IBD has decreased over the past 6 decades.**

Keywords: Inflammatory Bowel Diseases; Surgery; Systematic Review; Meta-analysis.

A recent systematic review indicated that the prevalence of inflammatory bowel disease (IBD) in Western countries is as high as 0.5% of the population and the incidence rate is as high as 20 per 100,000 persons for both Crohn's disease and ulcerative colitis.[1] Furthermore, the incidence of IBD has increased in many regions across the world.[1] The majority of patients with IBD are diagnosed in adolescence and early adulthood, but mortality is low.[1] Thus, developed nations can expect the burden of IBD to patients and the health care system to escalate with time.

The United States alone spends $6.1 billion annually on direct IBD health care costs.[2] One-third is due to hospitalizations,[2] with more than half of hospitalizations related to abdominal surgeries.[3] Intestinal resections for IBD significantly affect patients with respect to postoperative morbidity, mortality, quality of life, work productivity, and psychosocial deprivation.[4,5] Over the past 25 years, therapy for IBD has changed with the widespread use of immunosuppressive therapy (purine antimetabolites and methotrexate) and the introduction of anti–tumor necrosis factor (TNF) therapy.[6–9] The overall effectiveness of immunomodulators and anti-TNF in reducing surgery rates for IBD remains controversial.[10]

Furthermore, there is considerable debate in the literature as to whether the risk of surgery has decreased with time. Some studies have reported a decrease in surgical risk,[11–13] while others have reported no difference.[14–16] Understanding the evolution of surgical risk of IBD is important. It will allow clinicians to evaluate the cost-effectiveness of medical versus nonmedical interventions in management strategies, explore for heterogeneity in practice patterns across regions, and plan health care resource utilization.

Therefore, we conducted a systematic review and meta-analysis of population-based studies to investigate changes in the surgical risk of IBD over time and to define the 1-, 5-, and 10-year risk of surgery among patients with

Abbreviations used in this paper: CI, confidence interval; IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

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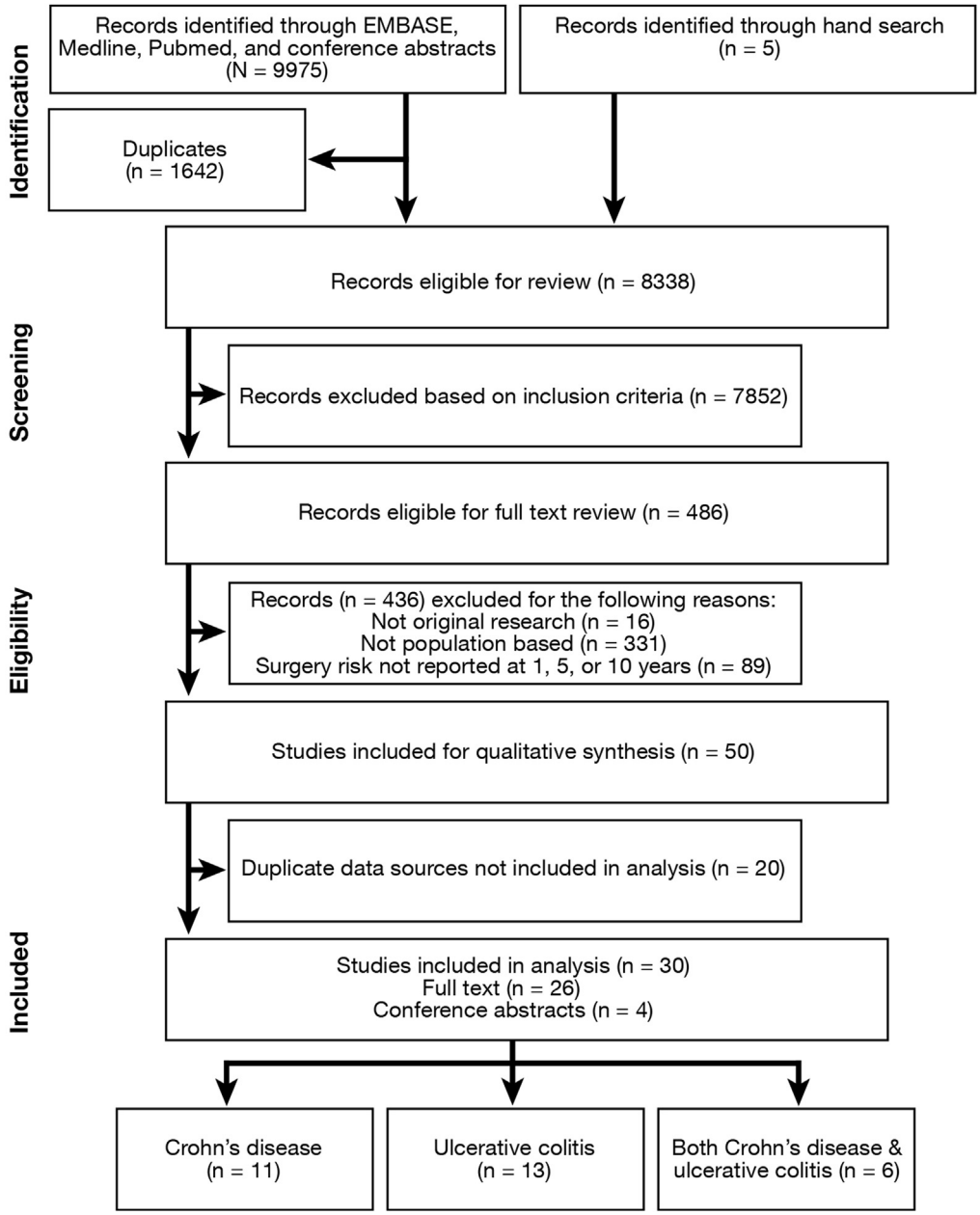

Figure 1. Details of study selection for review.

Crohn's disease and ulcerative colitis diagnosed in the last half of the 20th century.

Patients and Methods

Eligibility Criteria and Literature Search

We performed a systematic literature search using a predetermined protocol (Supplementary Appendix 1) and in accordance with the Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) guidelines and with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary Appendix 2).[17] We searched Medline, EMBASE (Excerpta Medica Database), and PubMed on May 8, 2013, for medical subheadings and key terms related to IBD and intestinal surgery. We additionally screened conference proceedings (2009–2012) of the American Gastroenterological Association, American College of Gastroenterology, United European Gastroenterology, and European Crohn's and Colitis Organization. An outline of the detailed search strategy is available in Supplementary Appendix 3. No restrictions were placed on language or publication date. Additionally, bibliographies of included articles were searched and experts in IBD were consulted to identify additional studies.

Selection Criteria

To be included, studies had to be originally researched and provide population-based estimates. Population-based studies were those that used probability sampling, studied the entire population of a defined area, or involved medical centers serving a population of known size. Studies had to report the calendar years that they collected information on incident cases and a 1-, 5-, or 10-year risk of surgery of Crohn's disease and/or ulcerative colitis.

Two reviewers (A.D.F. and J.D.) independently conducted an initial screen of abstracts for eligibility. Abstracts that were not

Table 1. Details of Studies Included in Meta-analyses of Cumulative Risk of Surgery in Patients With CD and/or UC

Study	Data source	Country	Disease	Sample size	Diagnosis (year)	Population	Outcome (year after diagnosis)
Jess et al, 2007[a,e,27,32,35,36,73]	Copenhagen County	Denmark	CD and UC	CD, n = 374;	1962–1987	Adults	1, 5, and 10
				UC, n = 1160	1991–1993	Adults	1, 5, and 10
				CD, n = 58;			
				UC, n = 89			
Benchimol et al, 2011[72]	Ontario Crohn's and Colitis Cohort	Canada	CD and UC	CD, n = 1662;	1994–2004	Pediatric	1, 5, and 10
				UC, n = 968			
Gheorghe et al, 2004[71]	Romania	Romania	CD and UC	CD, n = 85; UC,	2002–2003	Adults	1
				n = 163			
Vind et al, 2006[e,12,34,73]	Copenhagen City and County	Denmark	CD and UC	CD, n = 209;	2003–2005	Adults	1
				UC, n = 326			
Jakobsen et al, 2011[70]	Eastern Denmark, Funen, and Aarhus County	Denmark	CD and UC	CD, n = 65;	2007–2009	Pediatric	1
				UC, n = 62			
Niewiadomski et al, 2013[69]	Australia	Australia	CD and UC	CD, n = 43;	2010–2011	All ages	1
				UC, n = 30			
Bernell et al, 2000[e,26,52]	Stockholm County	Sweden	CD	n = 1921	1955–1989	All ages	1, 5, and 10
O'Keefe et al, 1989[53]	Cape Town	South Africa	CD	n = 72	1970–1979	All ages	5
				n = 53	1970–1979	All ages	10
Peyrin-Biroulet et al, 2012[28,45,54]	Olmsted County	United States	CD	n = 136	1970–1989	All ages	5 and 10
				n = 100	1990–1999		5 and 10
				n = 74	2000–2004		5
Lakatos et al, 2012[e,31,43,44,49,59]	Veszprem Province	Hungary	CD	n = 501	1977–2008	All ages	1, 5, and 10
Ramadas et al, 2011[13]	Cardiff	Wales	CD	n = 105	1986–1991	All ages	1 and 5
				n = 99	1992–1997	All ages	1 and 5
				n = 137	1998–2003	All ages	1 and 5
Nguyen et al, 2011[e,39,46]	University of Manitoba IBD Epidemiology Database	Canada	CD	n = 1364	1988–1995	All ages	1, 5, and 10
				n = 920	1996–2000	All ages	1, 5, and 10
				n = 1119	2001–2008	All ages	1 and 5
Peneau et al, 2012[b,c,e,29,42,55]	EPIMAD	France	CD	n = 538	1988–2004	Pediatric	1, 5, and 10
Henriksen et al, 2007[e,30,33,40,47,51]	IBSEN	Norway	CD	n = 200	1990–1993	All ages	5
Solberg et al, 2007[e,30,47]	IBSEN	Norway	CD	n = 197	1990–1993	All ages	1 and 10
Wolters et al, 2006[48]	EC-IBD	Denmark, Norway, The Netherlands, Ireland, Portugal, Greece, Israel, Spain, and Italy	CD	n = 316	1991–1993	All ages	10
Heresbach et al, 2004[50]	Abermad	France	CD	n = 63	1994–1997	Elderly	1 and 5
Leijonmarck et al, 1989[e,37,38,68]	Stockholm County	Sweden	UC	n = 1586	1955–1984	All ages	1, 5, and 10
Langholz et al, 1997[e,60,73]	Copenhagen	Denmark	UC	n = 80	1962–1987	Pediatric	1, 5, and 10
O'Keefe et al, 1989[61]	Cape Town	South Africa	UC	n = 91	1970–1979	All ages	5
				n = 61	1970–1979	All ages	10
Samuel et al, 2013[67]	Olmsted County	United States	UC	n = 80	1970–1979	All ages	1, 5, and 10[d]
				n = 96	1980–1989		
				n = 117	1990–1990		
				n = 76	2000–2004		

Table 1. Continued

Study	Data source	Country	Disease	Sample size	Diagnosis (year)	Population	Outcome (year after diagnosis)
Probert et al, 1993[62]	Leicestershire	England	UC	n = 691	1972–1989	All ages	5 and 10
Chow et al, 2009[56]	Prince of Wales Hospital	China	UC	n = 172	1985–2006	All ages	1 and 10
Targownik et al, 2012[a,e,41,64]	University of Manitoba IBD Epidemiology Database	Canada	UC	n = 858	1987–1991	All ages	1, 5, and 10
				n = 889	1992–1996		1, 5, and 10
				n = 930	1997–2001		1, 5, and 10
				n = 1075	2002–2008		1 and 5
Gower-Rousseau et al, 2009[57]	EPIMAD	France	UC	n = 113	1988–2002	Pediatric	1 and 5
Charpentier et al, 2012[b,66]	France	France	UC	n = 474	1988–2006	Elderly	1, 5, and 10
Malaty et al, 2011[b,65]	Texas	United States	UC	n = 112	1989–2003	Pediatric	1 and 5
Henriksen et al, 2006[e,30,40,51,58,63]	IBSEN	Norway	UC	n = 454	1990–1993	All ages	5
Solberg et al, 2009[e,30,63]	IBSEN	Norway	UC	n = 423	1990–1993	All ages	1 and 10
Lakatos et al, 2011[59]	Veszprem Province	Hungary	UC	n = 220	2002–2006	All ages	1 and 5

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.
[a]Additional data received from the investigators.
[b]Abstract as main data source.
[c]Abstract is an update of coreferenced manuscript.
[d]The 1- and 10-year risk was available for the entire study period (1970–2004) but not for subsets.
[e]Duplicate data sources coreferenced.

originally researched, did not include patients with IBD, or were not clearly population based were excluded. Two independent reviewers (A.D.F. and M.E.N.) evaluated the full-text articles of identified abstracts for final eligibility. Foreign language articles were translated before full-text assessment. Disagreements in full-text eligibility or data abstraction were resolved by consensus and, as necessary, involvement of a third party (G.G.K.).

Data Extraction and Quality Assessment

Reviewers independently extracted data from all studies that fulfilled the inclusion criteria. Data extracted included author; title; journal; year of publication; IBD type; data source; country; number of incident IBD cases; surgical risk at 1, 5, or 10 years after diagnosis; age of the population studied; and years of incident case collection. Key elements of study quality, adapted from previously published literature on assessing the quality of prevalence studies, were extracted.[18] Information on the population of interest and data acquisition methods was also extracted.

The outcomes of interest were surgical risk at 1, 5, and 10 years after diagnosis of IBD, defined as the proportion of patients undergoing surgery by a given time point. If the proportion was not provided, it was calculated by dividing the number of patients who underwent surgery by the total sample at the time point. We pooled crude, unadjusted estimates from all studies. Surgical risks at each time interval were considered separately for Crohn's disease and ulcerative colitis. Surgeries included any intestinal resection. Authors were contacted to supplement missing time point data. When multiple studies reported on the same data source, the study with the most comprehensive information was included (Table 1).

Statistical Analysis

We report the pooled surgical risk and 95% confidence intervals (CIs) at 1, 5, and 10 years for both Crohn's disease and ulcerative colitis. For time trend analyses (ie, assessing changes in surgical risk over time), the start year of inclusion of patients with incident Crohn's disease and/or ulcerative colitis was included as a continuous variable in a meta-regression model of all studies. Previous work comparing changes over time using start, midpoint, and end year showed that using start year as a continuous variable was the best approach to account for between-study variance.[19] When the slope of the surgery incidences fit by the mixed-effect model had an associated P value of $<.05$, we concluded that the incidence of surgery was changing significantly over time. We also stratified our temporal analysis by reporting the pooled 1-, 5-, and 10-year cumulative risk of surgery for studies with cases diagnosed post-1970 (1970–2011), post-1980 (1980–2011), post-1990 (1990–2011), and post-2000 (2000–2011).

We assessed for heterogeneity between studies using Cochran Q statistic and the I^2 statistic.[20,21] Due to the presence of heterogeneity, a random effects model was used. Meta-regression was performed to investigate potential sources of heterogeneity, other than time, including whether (1) a standardized data collection method was reported versus not reported, (2) the study was conducted in North America or Western Europe versus another geographic location, and (3) the study population was restricted to pediatric-onset IBD. Sensitivity analyses were performed excluding abstracts because the quality of the information could differ between abstracts and full-length articles. Publication bias was assessed by the Begg rank correlation test for asymmetry.[22]

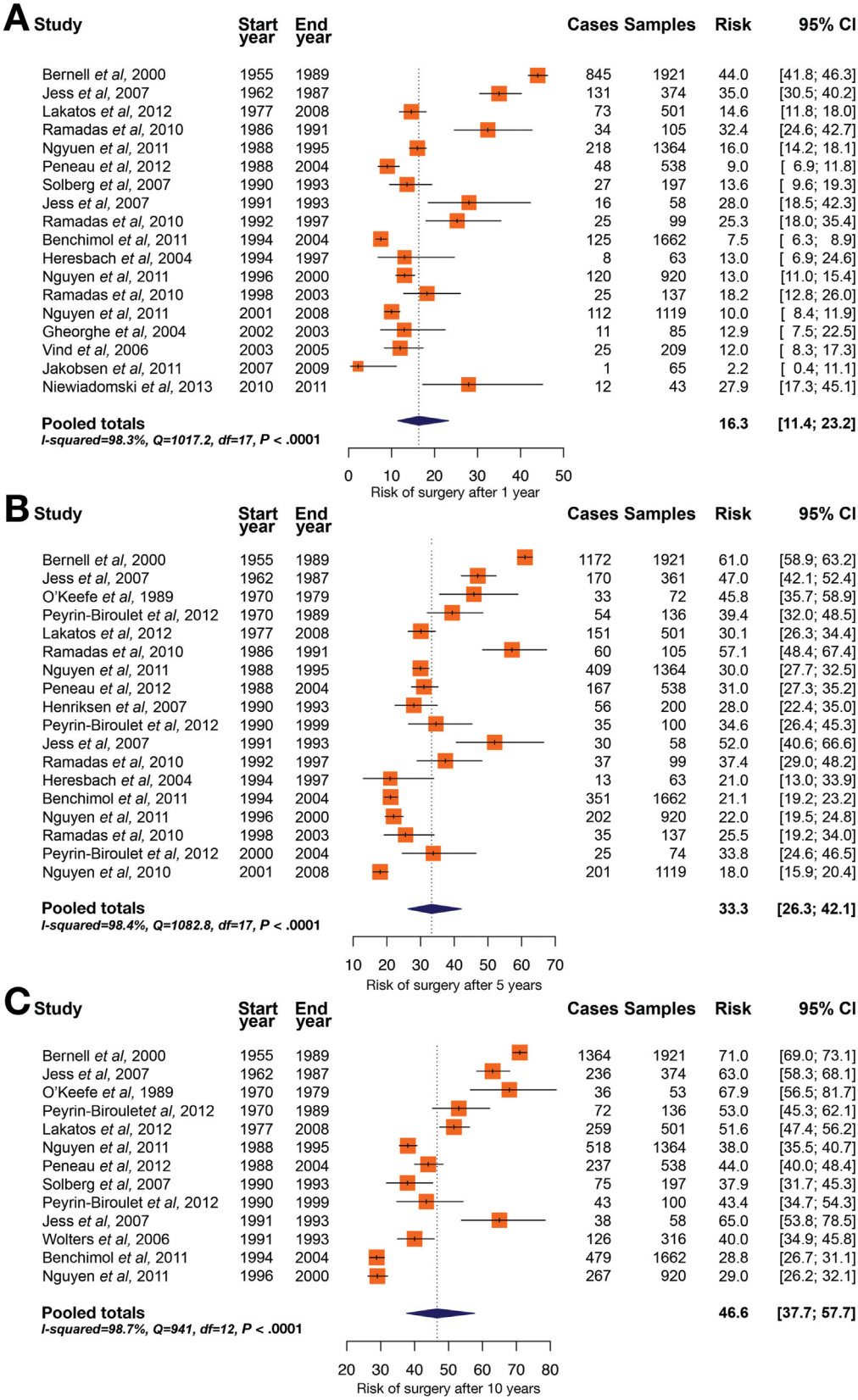

Figure 2. Forest plot using random effects models for all included studies for risk of surgery (*A*) 1 year, (*B*) 5 years, and (*C*) 10 years after diagnosis of Crohn's disease.

For all tests, a *P* value of <.05 was considered significant. All statistical analyses were performed using R version 2.14.[23] The meta package was used to produce the pooled estimates, forest plots, and publication bias assessment.[24] The metafor package was used to conduct the meta-regression using restricted maximum likelihood estimation.[25]

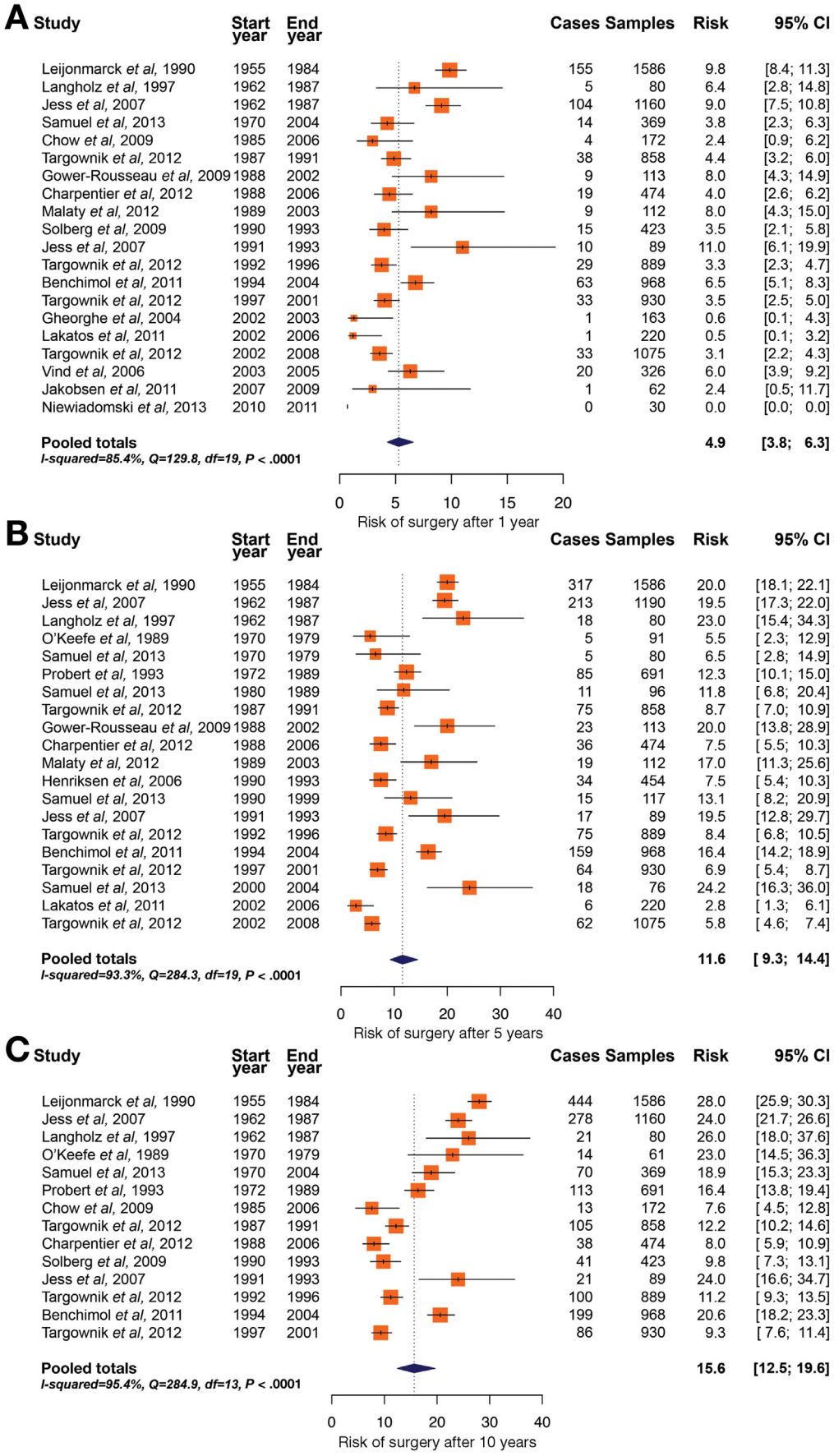

Figure 3. Forest plot using random effects models for all included studies for risk of surgery (*A*) 1 year, (*B*) 5 years, and (*C*) 10 years after diagnosis of ulcerative colitis.

Table 2. Risk of Surgery for Cases of Incident Crohn's Disease and Ulcerative Colitis Overall, Post-1970, Post-1980, Post-1990, and Post-2000

	Crohn's disease (95% CI)	Ulcerative colitis (95% CI)
All years of incident cases (after 1955)		
1-year surgery risk	16.3% (11.4%–23.2%)	4.9% (3.8%–6.3%)
5-year surgery risk	33.3% (26.3%–42.1%)	11.6% (9.3%–14.4%)
10-year surgery risk	46.6% (37.7%–57.7%)	15.6% (12.5%–19.6%)
Incident cases (after 1970)		
1-year surgery risk	14.8% (11.9%–18.3%)	4.4% (3.5%–5.5%)
5-year surgery risk	31.2% (26.6%–36.7%)	10.3% (8.2%–13.0%)
10-year surgery risk	43.4% (37.0%–50.9%)	13.5% (10.8%–16.9%)
Incident cases (after 1980)		
1-year surgery risk	14.8% (11.7%–18.7%)	4.4% (3.5%–5.6%)
5-year surgery risk	29.9% (24.9%–35.9%)	10.6% (8.2%–13.8%)
10-year surgery risk	39.1% (33.4%–45.8%)	11.9% (8.9%–15.9%)
Incident cases (after 1990)		
1-year surgery risk	14.3% (11.0%–18.6%)	4.1% (2.9%–5.7%)
5-year surgery risk	27.7% (22.8%–33.5%)	9.9% (6.9%–14.3%)
10-year surgery risk	38.7% (31.0%–48.3%)	13.7% (9.3%–20.3%)
Incident cases (after 2000)		
1-year surgery risk	12.6% (8.1%–19.5%)	2.7% (1.4%–5.3%)
5-year surgery risk	24.2% (13.1%–44.9%)	7.6% (2.5%–23.4%)
10-year surgery risk	NA	NA

NA, not available because there were no studies in this category.

Results

Literature Search

The search yielded 8338 unique citations, of which 486 met the criteria for full-text review (Figure 1). Of those, 436 were excluded because they did not report original research (n = 16), population-based estimates (n = 331), or 1-, 5-, or 10-year surgical risk (n = 89). Of the 50 remaining articles, 20 were excluded because they reported on the same data source.[26–45] Thirty studies were included for the final analysis; 26 were full-length manuscripts, and 4 were abstracts.

Details of Included Studies

Details of the included studies are shown in Table 1. The year of diagnosis of Crohn's disease and ulcerative colitis ranged from 1955 to 2011. The studies included 10,161 patients with Crohn's disease and 11,335 patients with ulcerative colitis from 20 different countries. Of the 30 studies, 11 reported on Crohn's disease,[13,46–55] 13 reported on ulcerative colitis,[56–68] and 6 reported on both diseases.[12,69–73]

Assessment of Study Quality

With the exception of the abstracts, all included studies clearly defined the target population, used probability sampling or surveyed the entire population, and used a sample that represented the target population. Seventeen of the 30 studies used standardized methods of data collection.

Trends in Risk of Surgery

Overall, the 1-, 5-, and 10-year risk of surgery in patients with Crohn's disease significantly decreased over time ($P < .05$) (Figure 2*A–C*). The risk of surgery for ulcerative colitis significantly decreased over time at 1 and 10 years ($P < .05$) but not at 5 years ($P = .06$) (Figure 3*A–C*). The same results were observed when abstracts were excluded for the sensitivity analyses.

The cumulative risk of surgery differed by the decade of diagnosis for studies conducted post-1970 (1970–2011), post-1980 (1980–2011), post-1990 (1990–2011), and post-2000 (2000–2011) (Table 2). For example, the pooled 1-, 5-, and 10-year risk of surgery in Crohn's disease was 14.3% (95% CI, 11.0%–18.6%), 27.7% (95% CI, 22.8%–33.5%), and 38.7% (95% CI, 31.0%–48.3%) among patients diagnosed after 1990. In ulcerative colitis, the 1-, 5-, and 10-year risk of surgery was 4.1% (95% CI, 2.9%–5.7%), 9.9% (95% CI, 6.9%–14.3%), and 13.7% (9.3%–20.3%) among patients diagnosed after 1990.

Sources of Heterogeneity and Publication Bias

Meta-regression was used to evaluate sources of heterogeneity in surgical risk other than time (Figure 4). The method of data collection was a significant source of heterogeneity for Crohn's disease at 10 years ($P = .03$). Studies with standardized data collection methods had lower surgical risk. Studies conducted in North America or Western Europe had significantly higher surgical risk at 1 and 5 years for ulcerative colitis ($P < .01$), whereas location of study did not significantly influence the surgical risk of Crohn's disease. Although surgical risk was lower in studies restricted to pediatric populations in Crohn's disease, this finding was only significant at 1 year ($P < .01$). In ulcerative colitis, surgical risk was significantly higher ($P = .02$) in pediatric populations at 5 years. Publication bias was not observed in any of the analyses ($P > .05$).

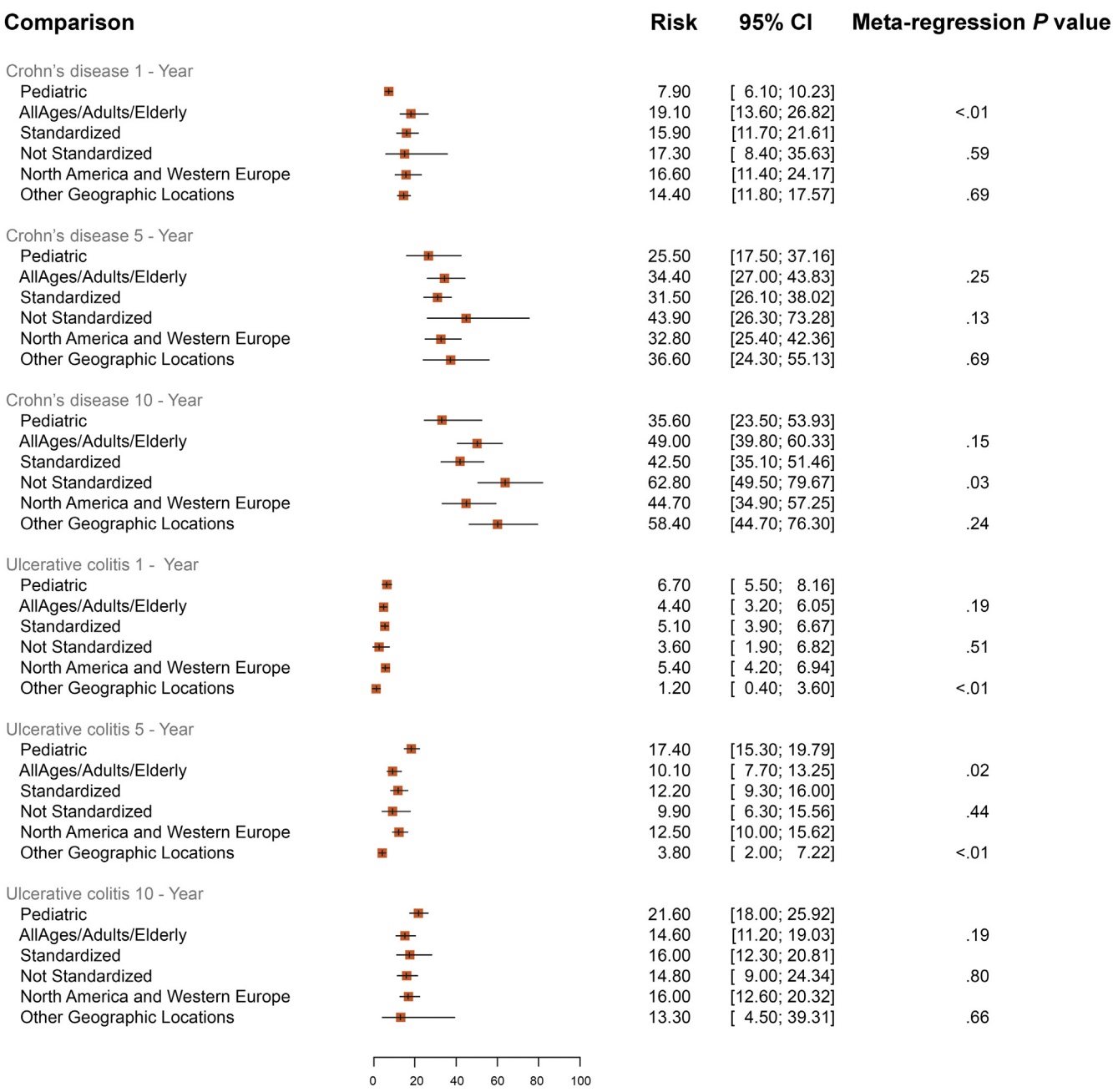

Figure 4. Stratified analyses of potential sources of heterogeneity in the assessment of the cumulative surgical risk at 1, 5, and 10 years after diagnosis of Crohn's disease and ulcerative colitis.

Discussion

In an era of rapidly changing medical therapy for IBD, it is paramount that we understand the evolution of surgical risk in both Crohn's disease and ulcerative colitis. This systematic review of 30 population-based studies comprehensively summarizes postdiagnostic surgical risk at 1, 5, and 10 years. Over the past several decades, the risk of surgery has significantly decreased in patients with Crohn's disease, whereas this finding was statistically significant at 1 and 10 years in patients with ulcerative colitis. These findings suggest that the natural history of IBD has evolved over the past 50 years such that patients with IBD diagnosed in the 21st century will experience fewer operations.

The reduction in surgery may be attributed to changes in practice patterns over time, including earlier disease detection, introduction of practice guidelines, promotion of continuing medical education for IBD, shift in care from surgeons to gastroenterologists, reduction in colectomies for dysplasia or colorectal cancer, and advocacy of patients through chapters of the Crohn's and Colitis Foundation.[74–79] Additionally, recent population-based studies have associated increasing and earlier use of immunomodulators with reduced surgery in patients with Crohn's disease and ulcerative colitis.[11,13,49] Randomized

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controlled trials have also shown that anti-TNF therapies reduce the need for surgery in patients with Crohn's disease and ulcerative colitis.[80,81] Thus, widespread and perhaps earlier use of immunomodulators and anti-TNF therapies may have contributed to the reduced risk of surgery in this meta-analysis. Because the true impact of introducing newer medical therapies cannot be ascertained in this meta-analysis, the temporal relationships between the introduction of newer therapies and declining surgical risks should be explored in future studies.[82]

The reduction of surgical risk of ulcerative colitis was not significant 5 years after diagnosis. This may be explained by the variability in the natural history of ulcerative colitis. The risk of surgery for ulcerative colitis is high within the first year of diagnosis due to patients who present with fulminant colitis. Advances in salvage therapies (eg, cyclosporine) for patients with fulminant ulcerative colitis refractory to intravenous corticosteroids may have resulted in fewer colectomies over time. In contrast, at 5 years after diagnosis, the indication for surgery is more often due to corticosteroid dependence or chronically active disease. The stable risk of colectomy 5 years after diagnosis may reflect inadequate maintenance therapies for patients with ulcerative colitis who were corticosteroid dependent. Future studies are necessary to evaluate whether the 5-year risk of colectomy has been influenced by the introduction of infliximab for ulcerative colitis in 2005. Ten years after diagnosis, dysplasia or cancer begins to drive the need for colectomy. Recent population-based studies have shown that the 10-year risk of dysplasia or cancer, and hence colectomies, is lower among patients with ulcerative colitis diagnosed in more recent decades.[79]

The limitations of this study should be considered. First, heterogeneity was observed across studies. Although we accounted for time in our meta-analysis, other issues of heterogeneity should be considered.[83] We explored the method of data collection, location of the study, and age of the population as potential sources of heterogeneity. However, no single factor we explored entirely explained heterogeneity. Second, the meta-analysis was not designed to identify the specific cause of the reduction in surgery. As such, any potential explanations for the reduction (such as increased use of immunomodulators over time) are ecological associations. Third, there is a dearth of population-based studies in pediatric-onset IBD, so we were unable to adequately explore a trend over time in this population. Finally, disease-specific information (eg, disease location) was often not available in most population-based studies.

Despite these limitations, this systematic review and meta-analysis showed that the risk of surgery for IBD is decreasing with time. This knowledge can assist with disease counseling and treatment planning. Clinicians and patients alike can use the summary statistics presented for 1-, 5-, and 10-year surgical risk over time to understand the probability of surgery within the first 10 years of diagnosis. Additionally, health care administrators can use these data for resource planning and health care allocation. This is particularly important in light of the evidence that the prevalence of IBD will likely increase steadily over time.[1] Furthermore, this information highlights important clinical gaps in the literature that should be addressed in future population-based studies and include evaluation of surgical risk in patients diagnosed after 2000, longer follow-up periods (eg, surgical risk 20 years after diagnosis), assessment of inflection points in time trend analyses that correlate to introduction of medical advances (eg, introduction of a new drug), and evaluation of surgical risk among patients with pediatric-onset IBD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2013.07.041.

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Conflicts of interest

The authors disclose the following: Dr deBruyn has served as an advisory board member for and received research funding from Janssen. Dr Panaccione has served as a speaker, a consultant, and an advisory board member for Abbott Laboratories, Merck, Schering-Plough, Shire, Centocor, Elan Pharmaceuticals, and Procter and Gamble; served as a consultant and speaker for AstraZeneca; served as a consultant and an advisory board member for Ferring Pharmaceuticals and UCB; served as a consultant for GlaxoSmithKline and Bristol-Meyers Squibb; served as a speaker for Byk Solvay, Axcan, Janssen, and Prometheus; has received research funding from Merck, Schering-Plough, Abbott Laboratories, Elan Pharmaceuticals, Procter and Gamble, Bristol-Meyers Squibb, and Millennium Pharmaceuticals; and has received educational support from Merck, Schering-Plough, Ferring Pharmaceuticals, Axcan, and Janssen. Dr Ghosh has served as a speaker for Merck, Schering-Plough, Centocor, Abbott Laboratories, UCB Pharma, Pfizer, Ferring Pharmaceuticals, and Procter and Gamble; participated in ad hoc advisory board meetings for Centocor, Abbott Laboratories, Merck, Schering-Plough, Proctor and Gamble, Shire, UCB Pharma, Pfizer, and Millennium Pharmaceuticals; received research funding from Procter and Gamble, Merck, and Schering-Plough; and Gilaad Kaplan research funding from served as a speaker for Janssen, Merck, Schering-Plough, Abbott Laboratories, and UCB Pharma; participated in advisory board meetings for Janssen, Abbott Laboratories, Merck, Schering-Plough, Shire, and UCB Pharma; and received research support from Merck, Abbott, and Shire. The remaining authors disclose no conflicts.

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