ORIGINAL ARTICLES



Risk of Cancers in Patients with Pediatric Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis

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Objectives We performed a systematic review and meta-analysis to evaluate the risk of the development of cancers in patients with pediatric-onset inflammatory bowel disease (IBD).

Study design A computerized literature search was performed. The primary outcome was the pooled incidence of cancer in studies reporting the risk as a standardized incidence ratio. The secondary outcomes were the pooled incidence rates of all cancers and site-specific cancers including colorectal cancer and hematologic cancers.

Results Sixty-six studies reporting outcomes in 38 092 patients were included. The pooled standardized incidence ratio for cancer was $2.39 \ (P < .0001, 95\% \text{ Cl } 2.00-2.86)$ in IBD. The pooled incidence rates for cancer in patients with Crohn's disease (CD) and ulcerative colitis (UC) were $0.014 \ (95\% \text{ Cl } 0.0087-0.021)$ and $0.031 \ (95\% \text{ Cl } 0.018-0.052)$, respectively. The pooled incidence rate of colorectal cancer in CD and UC were $0.0075 \ (95\% \text{ Cl } 0.0049-0.011)$ and $0.020 \ (95\% \text{ Cl } 0.012-0.034)$, respectively. The pooled rates of hematologic cancers in CD and UC were $0.0061 \ (95\% \text{ Cl } 0.0040-0.0090)$ and $0.0045 \ (95\% \text{ Cl } 0.0026-0.0079)$, respectively. Cumulative meta-analyses showed a decreasing trend in the incidence of these cancers in both CD and UC.

Conclusions Patients with pediatric-onset IBD had an increased risk of cancer development compared with the general population, however, incidence appeared to be decreasing in recent years. (*J Pediatr 2021;229:102-17*).

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he incidence of childhood-onset inflammatory bowel disease (IBD) is increasing,¹ therefore, understanding the risks of the disease complications, including cancer development, is essential in providing adequate care throughout the transition from pediatric to adult IBD.

Chronic inflammation is a known risk factor for the development of cancer in IBD. Beyond the recognized association between IBD and the increased risk of colorectal cancer (CRC),² recent data have expanded the concept to inflammation as a driver of tumor progression.³ In addition, the increasingly widespread use of immunosuppressive therapies in the management of Crohn's disease (CD) and ulcerative colitis (UC) raises concerns about the risk of cancer development secondary to such therapies. Immunosuppressive therapies increase the risk of lymphoma and skin cancer in transplant recipients as well as patients with rheumatoid arthritis and psoriasis.⁴

There have been some reports that cancers were more likely to occur in patients with pediatric-onset IBD.^{5,6} A previous metaanalysis provided an overview of patients with IBD diagnosed at pediatric age who developed cancer or suffered a fatal outcome at any point later in life.⁷ However, the risk of cancer development in patients with pediatric-onset IBD remains largely unknown, in spite of the risk of cancer development including CRC^{8,9} and lymphoma¹⁰ in patients with adult-onset IBD has been previously identified. In addition, we sought to find out the frequency of cancer and the relationship with background factors of cancer in childhood-onset IBD, which have not been studied in detail in the previous meta-analysis. In the present systematic review and meta-analysis, we aimed to assess the risk of cancer development in patients with IBDs diagnosed in their childhood.

CD	Crohn's disease
CRC	Colorectal cancer
IBD	Inflammatory bowel disease
RCT	Randomized controlled trial
SEER	Surveillance, epidemiology, and end result
SIR	Standardized incidence ratio
TNF	Tumor necrosis factor
UC	Ulcerative colitis

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Methods

We performed this study according to a priori defined protocol and in accordance with the PRISMA guidelines and Meta-Analysis of Observational Studies in Epidemiology guidelines.^{11,12} The protocol of this meta-analysis has been registered to International prospective register of systematic reviews (PROSPERO¹³ CRD42017076264).

Data Sources

A computerized literature search was performed on PubMed/ MEDLINE, Google Scholar, Scopus, EMBASE, and Cochrane Central Register of Controlled Trials (inception to June 30, 2018). An update literature search was undertaken on April 30, 2020 for PubMed/MEDLINE, Google Scholar, Scopus, and Cochrane Central Register of Controlled Trials. For Google Scholar, only the first 1000 articles were reviewed in each search, as it does not provide results beyond it. We also searched abstracts from medical conferences (Digestive Disease Week, American College of Gastroenterology, United European Gastroenterology Week, European Crohn's and Colitis Organisation, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, American Society of Hematology, European Hematology Association, American Society of Clinical Oncology, European Cancer Congress) and bibliographies of identified articles for additional references (inception to April 30, 2020).

Search Strategy and Study Selection

To be eligible for inclusion, we considered prospective and retrospective studies evaluating the risk of cancer development in patients with IBD diagnosed prior to age 18 years (further referred to as pediatric IBD).¹⁴ Studies were eligible if the included subjects were of a pediatric population (age <18 years) or an adolescent (age ≤25 years) as well as childhood population with the majority of the included subjects less than age 18 years. Studies were required to report outcomes specifically for IBD, CD, UC, or indeterminate colitis. There were no restrictions regarding date of study, sex of the subjects, or duration of the study. We imposed no geographic or language restrictions and articles in languages other than English were translated if necessary. Two authors independently screened each of the potential titles, abstracts, and/or full-manuscripts to determine whether they were eligible for inclusion. Studies were initially excluded based on their title. Next, the abstract or full text were reviewed to assess eligibility. Areas of disagreement or uncertainty were resolved by consensus among the authors. The corresponding authors of studies were contacted to provide additional information on studies if required. Studies were identified with the terms: "inflammatory bowel disease," "Crohn's disease," or "ulcerative colitis." These were combined by using the set operator AND with studies identified with the terms: "pediatric*," "childhood," "cancer*," "malignancy*," "colorectal cancer*," "hematologic cancer*," "Hodgkin's lymphoma," "non-Hodgkin's lymphoma," "lymphoma," and "leukemia" (both as medical subject headings and free text terms). Details of PubMed/MEDLINE search is shown in **Table I** (available at www.jpeds.com), as one of the search strategies. PRISMA flow diagram, describing the number of studies identified from the search strategy and retained at each stage, is described in **Figure 1** (available at www.jpeds.com).

Data Extraction and Quality Assessment

All data were independently extracted in duplicate by 2 authors by using a data extraction form. The 2 authors' data extraction were found to be consistent. Data on the study characteristics, such as author name, year of publication, country, sample size, age of patients, comorbidity, outcome, and incidence of adverse effects, were collected. The Jadad score¹⁵ and Cochrane Risk of Bias Assessment Instrument,¹⁶ a scale that assesses the methodological quality of a clinical trial, were used to assess the quality of randomized controlled trials (RCTs). The Newcastle-Ottawa Scale was used to assess the quality of the observational studies.¹⁷ Star rating of 0-9 was allocated to each study based on 3 parameters (selection, 0-4; comparability, 0-2; and outcome, 0-3). Studies receiving 6 or more stars are considered high quality.^{18,19} The overall quality and the risk of bias level in this systematic review were assessed using the GRADE criteria (Grading of Recommendations Assessment, Development and Evaluation)²⁰ using GRADEpro.²¹

Outcome Assessment

The primary outcome of interest was the pooled risk of cancer development among studies that reported the risk as a standardized incidence ratio (SIR). The secondary outcome of interest was the pooled incidence rates of all cancers and site-specific cancers including CRC and hematologic cancers (Hodgkin's lymphoma, non-Hodgkin's lymphoma, and leukemia). We conducted subgroup meta-analyses for each assessment. In addition, we performed meta-regression analyses to evaluate whether incidences of cancer were influenced by medication type. We also assessed temporal trends in the risk of cancers by cumulative meta-analyses. The secondary outcomes except for the pooled incidence rates of all cancers and site-specific cancers deviated from the registered PROSPERO protocol: these outcomes were determined to be necessary for this study after registration to PROSPERO.

Statistical Analyses

Random-effects meta-analysis was performed to assess the risk of cancer development among patients with pediatric IBD. We evaluated the presence of heterogeneity across trials of each therapy by using the I^2 statistic. $I^2 < 25\%$ indicates low heterogeneity, 25%-75% moderate heterogeneity, and >75% high heterogeneity.²² Statistic Q (Q) was also used with a probability (P) value of <.10 as evidence of statistically significant heterogeneity.²³ We conducted subgroup meta-analyses, which were performed for both CD and UC, or meta-regression to examine potential sources of heterogeneity, where indicated, with factors such as age, sex, disease duration, and concomitant anti-tumor necrosis factor

(TNF) agents or immunomodulator use. Accompanying each meta-regression, we also did the analyses of variance to find whether the amount of total variance was more than we would expect based on within-study error or not.²⁴ To assess the potential for small-study effect and publication bias, we performed Begg and Egger tests and constructed funnel plots to visualize possible asymmetry when 3 or more studies were available.^{25,26} In addition, we conducted cumulative meta-analysis ranked by year to explore the temporal trend of the summary estimate. The temporal change of the cumulative meta-analysis was assessed by univariate regression analyses to evaluate whether the change was significant. In addition, influence analyses, by removing individual studies from the meta-analyses to assess the influence of any particular study on the results, and meta-analyses excluding studies with less than 30 patients were performed to assess the robustness of our results. All statistical analyses were performed with Comprehensive Meta Analysis V2 (Biostat, Englewood, New Jersey). P values that were <.05 were considered statistically significant except for the Q statistic P value. All statistical tests were 2-sided.

Results

Study Characteristics

We identified 969 127 citations through literature search and excluded 968 806 citations after initial screening of titles and abstracts; 321 full-text studies were evaluated for eligibility. After final review, 66 full text articles, including 38 092 patients were included in our analysis (Figure 1). Among the 66 studies, 44 studies included patients with CD, 31 studies included patients with UC, and 5 studies reported data on patients with IBD with no distinction made between CD or UC. Fourteen studies included data on both CD and UC. Fifty (75.76%) of the studies included patients under 18 years at diagnosis of IBD, and the remainder of the studies included patients who were aged 18-24 years at diagnosis. Thirty studies specified that the cancer occurred in childhood. Among 62 observational studies, 14 studies received 6 or more stars in the assessment by the Newcastle-Ottawa Scale, but the rest of the studies received 2 to 5 stars. Among 4 RCTs, all RCTs received 3 or 2 points in the assessment by the Jadad score. The quality of RCTs was also assessed by Cochrane Risk of Bias Assessment Instrument (Table II; available at www.jpeds.com). There was no inter-rater disagreement for the extracted data between the two authors. The characteristics and outcomes of the included studies are summarized in Table III. A summary of findings table (Table IV; available at www.jpeds.com) was created and exported from GRADEpro.

Meta-Analysis of the Overall Risk of Cancer Reported as SIR among Patients with Pediatric IBD

Six retrospective observational studies including more than 17 450 patients reported the overall risk of cancer as an SIR. Four studies reported outcome in both CD and UC. Two studies did not differentiate between CD and UC and one of these reported outcomes separately for patients exposed to biologic therapy (anti-TNF α agents) or not. Among 17 450 patients from 6 retrospective observational studies where SIR was reported, at least 125 patients developed malignancy, though 1 paper did not report the specific number of patients with malignancies. As shown in **Figure 2**, A, 4 studies included patients with CD and demonstrated a 2.4-fold increased risk of cancers (pooled SIR 2.42, P < .0001, 95% CI 1.90-3.06) with low heterogeneity ($I^2 = 0$ %). Five studies included patients with UC and also demonstrated a 2.1-fold increased risk of cancers (pooled SIR 2.10, P < .0001, 95% CI 1.51-2.90) with moderate heterogeneity ($I^2 = 41.54$ %).

The pooled SIR including all patients with pediatric IBD was 2.39 (P < .0001, 95% CI 2.00-2.86) with low heterogeneity ($I^2 = 0\%$) (Figure 2, A). Visual inspection of the funnel plot demonstrated no asymmetry and there were no smallstudy effects or publication biases as assessed by the Begg and Egger tests (P = .35, .30, respectively; Figure 2, B).

Meta-Analysis of Incidence Rates of Overall Cancer Development among Patients with Pediatric IBD

The pooled incidence rate of cancer occurrence was analyzed from 9 prospective and 44 retrospective studies (1 study included both study designs) with a total of 32 417 patients with pediatric IBD.

As shown in Figure 3, A, the pooled incidence rate of overall cancers in CD was 0.014 (95% CI 0.0087-0.021) with high heterogeneity $(I^2 = 78.90\%)$. The pooled incidence rate of cancers in patients with UC was 0.031 (95% CI 0.018-0.052) with high heterogeneity $(I^2 = 91.59\%)$ (Figure 3, A). The pooled incidence rate of overall cancers among all included studies was 0.018 (95% CI 0.013-0.025) with high heterogeneity $(I^2 = 89.10\%)$ (Figure 3, A). Meta-regression showed that there was a positive correlation between the follow-up duration of the studies and the risk of overall malignancy (regression coefficient 0.014, 95% CI 0.0011-0.017, P < .0001) (Figure 3, B). Analyses of variance showed that Qe was not statistically significant (Qe = 46.01, P = .050), indicating that heterogeneity was largely explained by this factor, and that there remained no statistically significant heterogeneity once follow-up duration has been taken into consideration. According to meta-regression analyses, the risk of overall cancer development was not particularly affected by the history of concomitant medications such as steroid, immunomodulator and anti-TNF agents (Tables V-VII; available at www.jpeds.com). There were small-study effects or publication biases as assessed by the Begg and Egger tests (P = .00072, .00060, respectively), but visual inspection of the funnel plot appeared to show no asymmetry (Figure 3, C). Funnel plots of the studies reporting the risk of overall cancers among patients with CD and UC were also shown in Figure 4, B, D, respectively (available at www.jpeds.com).

				Patient		Age at diagnosis or		Age at diagnosis of	Follow up		ncomita cations		Numbers of patients with	SIR of overall	Numbers of			of patier gic can			
ases	Author	Year (reference*)	Study design	numbers (n)	Age at diagnosis (y)	onset (y, mean)	Age at study (y, mean)	cancers (y, median) [†]	Follow-up duration (mean, mo)	Steroids	AZA, 6 MP	Anti- TNFα	overall cancers (n)	cancers (95% CI)	Numbers of patients with CRC	Overal	HL	NHL	Leukemia	Newcastle- Ottawa scale [‡]	
	Weedon et al ¹	1973	Retrospective	449	1-21 [§]	14.9	NA	NA (34 at diagnosis of CRC)	NA	NA	NA	NA	12	NA	8	NA	NA	NA	NA	2 (S:1, C:0, 0:1))
	Postuma et al ²	1985	Retrospective	33	6-16	13.0	NA	12	28.2	48	NA	NA	1	NA	0	1	NA	NA	0	5 (S:2, C:0, 0:3)	
	Verhave et al ³	1990	Retrospective	12	11-16 [§]	NA	14.0	-	24	NA	100	NA	0	NA	0	0	0	0	0	1 (S:0, C:0, 0:1)	
	Gold et al ⁴	1993	Retrospective	15	5.5-22.5 [§]	NA	15.5 [¶]	-	NA	NA	NA	NA	0	NA	0	0	0	0	0	1 (S:0, C:0, 0:1)	
	Gillen et al ⁵	1994	Retrospective	113	15-25	NA	NA	40	NA	NA	NA	NA	NA	NA	4	NA	NA	NA	NA	1 (S:1, C:0, 0:0)	
	Gryboski et al ⁶	1994	Retrospective	40	≤10	7.5	NA	NA	78	95	NA	NA	1	NA	0	0	0	0	0	2 (S:0, C:0, 0:2)	
	Langholz et al ⁷	1997	Retrospective	23	<15	11.0	NA	-	NA	NA	NA	NA	0	NA	0	0	0	0	0	3 (S:3, C:0, 0:0))
	Markowitz et al ⁸	2008	Prospective (RCT)	55	<18 [§]	NA	13.0	-	18**	100	49	NA	0	NA	0	0	0	0	0	NA	
	Stephens et al ⁹	2003	Retrospective	82	5-23 [§]	NA	15.3	-	NA	49	95	100	0	NA	0	0	0	0	0	4 (S:3, C:0, 0:1))
	de Ridder et al ¹⁰	2004	Retrospective	30	2.7-16.8	11.4	NA	-	25.3	60	90	100	0	NA	0	0	0	0	0	6 (S:3, C:0, 0:3)	,)
	Hyams et al ¹¹	2007	Prospective (RCT)	112	6-17 [§]	NA	13.3	-	11.0	35	89	100	0	NA	0	0	0	0	0	NA	
	de Ridder et al ¹²	2008	Retrospective	66	<19 [§]	12.2	NA	-	41.3	12	64	100	0	NA	0	0	0	0	0	4 (S:2, C:0, 0:2)	:)
	Vernier- Massouille et al ¹³	2008	Retrospective	404	<17	14.0	NA	-	84.0	85	61	24	0	NA	0	0	0	0	0	6 (S:3, C:0, 0:3))
	Duricova et al ¹⁴	2009	Retrospective	82	8-18	NA	14.5	-	33.0	NA	91	100	0	NA	0	0	0	0	0	5 (S:2, C:0, 0:3))
	Hyams et al ¹⁵	2009	Prospective	128	NA	NA	12.7 ^{††}	14	42.0	52	90	100	1	NA	0	1	1	0	0	5 (S:3, C:0, 0:2)	n
	Jakobsen et al ¹⁶	2009	Retrospective	9	<15	12.0	NA	-	NA	NA	0	0	0	NA	0	0	0	0	0	6 (S:2, C:2, 0:2)	
	Ruemmele et al ¹⁷	2009	Prospective (RCT)	40	7-17	NA	13.9	-	14.0	100	93	100	0	NA	0	0	0	0	0	NA	
	Viola et al ¹⁸	2009	Prospective	23	9-20	12.0	16.1	-	12.0	78	48	100	0	NA	0	0	0	0	0	2 (S:0, C:0, 0:2)	1)
	Pigneur et al ¹⁹	2010	Retrospective	206	<16	13.0	NA	NA	NA	96	72	26	5	NA	3	NA	NA	NA	NA	4 (S:3, C:0, 0:1)	
	Sinitsky et al ²⁰	2010	Retrospective	16	1.8-17.5 [§]	NA	13.0**	-	28.0	44	94	100	0	NA	0 0	0	0	0	0	4 (S:1, C:0, 0:3)	
	Crombé et al ²¹	2011	Retrospective	120	<17	14.5	NA	30	32.0	82	38	100	1	NA	0	ő	Ő	Ö	Ő	5 (S:2, C:0, 0:3)	
	Hyams et al ²²	2011	Prospective	60	6-17	NA	13.2	-	23.0	37	90	100	0	NA	Ő	õ	Õ	0	Õ	3 (S:1, C:0, 0:2)	
	Kelsen et al ²³	2011	Retrospective	20	≤7	NA	6.2 ^{¶,††}	-	NA	NA	NA	100	õ	NA	0	ŏ	Ő	Ö	õ	2 (S:1, C:0, 0:1)	
	Ashworth	2012	Retrospective	791	/ ≤21 ^{##}	12.4	NA	12	NA	NA	73	30	NA	NA	NA	1	0	1	0	6 (S:3, C:0, 0:3)	
	et al ²⁴ De Greef	2012	Prospective ^{§§} ,	104	≤17	13.2	NA	-	45.0	NA	75	100	0	NA	0	0	0	0	0	4 (S:2, C:0, 0:2)	2)
	et al ²⁵ Hyams et al ²⁶	2012	retrospective Prospective	188	6-17	NA	13.6	-	12.0	38	62	100	0	NA	0	0	0	0	0	NA	
	Kierkus et al ²⁷	2012	(RCT) Prospective	66	NA	8.4	14.1		2.5	NA	NA	100	0	NA	0	0	0	0	0	1 (S:0, C:0, 0:1)	
	Assa et al ²⁸	2012	Retrospective	102	-18	0.4 11.3	14.1 NA	-	Z.5 NA	NA	NA	100	0	NA	0	0	0	0	0	2 (S:0, C:0, 0:1)	
	Jess et al ²⁹	2013	Retrospective	115	≤10 ≤19	NA NA	NA	NA	195.0	NA	NA			2.17 (1.21-3.90)	NA	NA	NA	NA	NA	7 (S:2, C:2, 0:3)	
	Navas-López et al ³⁰	2013	Retrospective	16	NA	10.6	NA	17	NA	6	88	100	1	NA NA	0	1	0	1	0	2 (S:0, C:0, 0:2)	
	Peneau et al ³¹	2013	Retrospective	538	<17	14.6	NA	15 [¶]	134.0	36	NA	NA	6	2.50 (0.80-5.80)	1	1	0	0	1	7 (S:3, C:2, 0:2)	()
	Kappelman et al ³²	2014	Retrospective	NA	≤19	NA	NA	NA	NA	NA	NA			2.30 (1.53-3.46)	NA	NA	NA	NA	NA	6 (S:2, C:2, 0:2)	
	Nuti et al33	2014	Retrospective	78	8-23	NA	15.0	-	36	NA	54	100	0	NA	0	0	0	0	0	3 (S:1, C:0, 0:2)	
	Rosh et al ³⁴ Vahabnezhad	2014 2014	Retrospective	192	NA***	NA 11.0	NA NA	- NA	NA 60	NA 36	NA 21	100 100	0 1	NA NA	0	0 1	0	0 NA	0 NA	2 (S:1, C:0, 0:1)	
	et al ³⁵	2014	Retrospective	157	≤21	11.0	NA	IWA	00	30	21	100	1	NA	U	1	NA	INA	NA	3 (S:1, C:0, 0:2)	1
	Fumery et al ³⁶ Hyams et al ³⁷	2015 2017	Retrospective Retrospective	27 4047	<17 <17	11.0 9.9 ⁺⁺⁺	15.0 12.3 ¹¹¹	- NA	16.0 19.2 ¹¹¹	19 NA ^{†††}	7 67 ^{†††}	100 67 ¹¹¹	0 12	NA 2.43 (1.29-4.15) ^{†††}	0 0	0 7	0 1	0 4	0 2	5 (S:2, C:0, 0:3) 7 (S: 4, C:1,)
		0017			11.00	15.5			0.0	75	100				0	0	0	0	0	0:2)	
	Mallet et al ³⁸ Olen et al ³⁹	2017 2017	Retrospective	4 3768	11-20 <18	15.5 14.0	NA 30.0	- NA	3.8 NA	75 NA	100 28	NA 8 4	0	NA NA	0 17	0 12	0 NA	0 NA	0 NA	4 (S:2, C:0, 0:2)	
	Choi et al ⁴⁰	2017	Retrospective Retrospective	3768	<18 9.1-15.6	14.0	30.0 NA	INA	NA	NA	28	8.4 100	153 0	NA	0	0	0 0	NA 0	NA 0	8 (S:4, C:2, 0:2) 1 (S:0, C:0, 0:1)	

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Diseases				Patient		Age at diagnosis or		Age at diagnosis of	Follow-up		comita cations		Numbers of patients with	SIR of overall	Numbers of	Num her		gic can			
	Author (Year (reference*) Study design	numbers (n)	Age at diagnosis (y)	onset (y, mean)	Age at study (y, mean)	cancers (y, median) [†]	duration (mean, mo)	Steroids	AZA, 6 MP	Anti- TNFα	overall	cancers (95% CI)	patients with CRC	Overal	I HL	NHL	Leukemia	Newcastle- Ottawa scale [‡]	Jadad score
	Fang et al ⁴¹	2018	Retrospective	39	0-6	1.2 [¶]	NA	-	NA	NA	NA	NA	NA	NA	NA	NA	0	0	NA	5 (S:2, C:0, 0:3)	
	Turner et al ⁴² Malham et al ⁴³	2018 2019	Retrospective Retrospective	881 2921	6-17 <18	NA 14.0	15.0 NA	- NA	33.6 114.0	NA NA	43 NA	57 NA	0 33	NA 2.6 (1.8-3.7)	0 4	0 6	0 4	0 1	0 NA	1 (S:0, C:0, 0:1) 8 (S:4, C:2, 0:2)	
	Olén et al ⁴⁴	2020	Retrospective	1385	<18	NA	NA	NA	NA	NA	NA	NA	NA	NA	4	NA	NA	NA	NA	8 (S:4, C:2, 0:2)	
UC	^{‡‡‡} Ladd et al ⁴⁵	1935	Detroppetive	26	≤12	NA	NA	13	NA	NA	NA	NA	1	NA	1	0	0	0	0	0 (S:0, C:0, 0:0)) NA
00	Lagercrantz	1955	Retrospective Retrospective	137	≤12 ≤15	NA	NA	NA	NA	NA	NA	NA	NA	NA	6	NA	NA	NA	NA	2 (S:0, C:0, 0:0)	
	et al ⁴⁶	1050	Determention	10	45	8.9 ^{§§§}		01							014					0/00 00 00	
	Holowach et al ⁴⁷	1956	Retrospective	18	<15	0.9000	NA	21	NA	NA	NA	NA	NA	NA	214	NA	NA	NA	NA	0 (S:0, C:0, 0:0)) NA
	Michener	1961	Retrospective	427	≤13	11.1	NA	NA	NA	NA	NA	NA	NA	NA	46	NA	NA	NA	NA	1 (S:0, C:0, 0:1)) NA
	et al ⁴⁸ Hijmans et al ⁴⁹	1962	Retrospective	43	≤16	9.1	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	0 (S:0, C:0, 0:0)) NA
	Korelitz et al50	1962	Retrospective	134	≤15	11.0	NA	NA	NA	NA	NA	NA	9	NA	5	0	0	0	0	1 (S:0, C:0, 0:1)) NA
	Skyring et al ⁵¹	1965	Retrospective	80	≤15	7.2 ^{§§}	NA	NA (17 at diagnosis of CRC)	NA	NA	NA	NA	3	NA	2	0	0	0	0	1 (S:1, C:0, 0:0)) NA
	Devroede et al ⁵²	1971	Retrospective	396	<15	NA	NA	NA	NA	NA	NA	NA	52	NA	NA	NA	NA	NA	NA	0 (S:0, C:0, 0:0)) NA
	Patterson	1971	Retrospective	43	<20 [§]	14.0	NA	28	NA	72	NA	NA	2	NA	1	0	0	0	0	1 (S:0, C:0, 0:1)) NA
	et al ⁵³ Binder et al ⁵⁴	1972	Retrospective	44	<16 [§]	10.0	NA	NA	60.8	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	2 (S:1, C:0, 0:1)) NA
	Michener et al ⁵⁵	1979	Retrospective	336	≤20	15.0 ^{§§}	NA	NA	142.0	NA	NA	NA	10	NA	9	1	NA	NA	NA	3 (S:1, C:0, 0:2)	
	Verhave et al ³	1990	Retrospective	9	3.5-17 [§]	NA	14.0	-	24.0	NA	100	NA	0	NA	0	0	0	0	0	1 (S:0, C:0, 0:1)	
	Ahsgren et al ⁵⁶	1993	Retrospective	32	≤19 5 5 00 5 [§]	14.0	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	2 (S:1, C:0, 0:1)	
	Gold et al ⁴ Hvams et al ⁵⁷	1993 1996	Retrospective Retrospective	4 171	5.5-22.5 [§] <18	NA 11.1	15.5 [¶] NA	- 25	NA 61.2	NA 33	100 2	NA NA	0 2	NA NA	0 2	0	0 0	0 0	0 0	1 (S:0, C:0, 0:1) 4 (S:1, C:0, 0:4)	
	Langholz et al ⁷	1997	Retrospective	80	<15	10.0	NA	NA	NA	NA	ŇA	NA	1	NA	1	0	0	0	0	3 (S:3, C:0, 0:4)	
	Falcone et al58	2000	Retrospective	73	<18	11.3	NA	NA	48.4	NA	5	NA	NA	NA	0	NA	NA	NA	NA	4 (S:1, C:0, 0:2)) NA
	Gower- Rousseau et al ⁵⁹	2009	Retrospective	113	<17	14.0	NA	28	77.0	82	25	1	NA	NA	1	NA	NA	NA	NA	6 (S:3, C:0, 0:3)) NA
	Jakobsen et al ¹⁶	2009	Retrospective	60	<15	11.0	NA	NA	NA	38	0	0	2	NA	2	0	0	0	0	6 (S:2, C:2, 0:2)) NA
	Hyams et al ⁶⁰	2010	Retrospective	52	<16	12.2	NA	-	30.0	90	42	100	0	NA	0	0	0	0	0	5 (S:3, C:0, 0:2)	
	Kelsen et al ²³	2011	Retrospective	4	≤7 ≤21 ^{‡‡}	NA	6.2 ^{¶,††}	-	NA	NA NA	NA	100	0	NA NA	0 NA	0 1	0 1	0 0	0	2 (S:1, C:0, 0:1)	
	Ashworth et al ²⁴	2012	Retrospective	535	521	12.7	NA	18	NA	NA	45	12	NA	NA	NA	I	1	U	0	6 (S:3, C:0, 0:3)) NA
	Jess et al ²⁹	2013	Retrospective	153	≤19	NA	NA	NA	225.0	NA	NA	NA	9	1.16 (0.57-2.37)	NA	NA	NA	NA	NA	7 (S:2, C:2, 0:3)	
	Peneau et al ³¹ Kappelman	2013 2014	Retrospective Retrospective	160 NA	<17 ≤19	14.5 NA	NA NA	15 [¶] NA	139.0 NA	27 NA	NA NA	NA NA	3 NA	4.60 (0.90-13.50) 2.00 (1.44-2.78)	1 NA	0 NA	0 NA	0 NA	0 NA	7 (S:3, C:2, 0:2) 6 (S:2, C:2, 0:2)	
	et al32		·											. ,							
	Vahabnezhad et al ³⁵	2014	Retrospective	31	≤21	12.0	NA	NA	47.0	65	29	100	0	NA	0	0	0	0	0	3 (S:1, C:0, 0:2)	
	Hyams et al ³⁷	2017	Retrospective	1432	<17	9.9***	12.3	NA	19.2	NA	67	67	3	2.43 (1.29-4.15)***	0	2	0	1	1	7 (S: 4, C:1, 0:2)	NA
	Olén et al ³⁹	2017	Retrospective	4648	<18	14.0	30.0	-	NA	NA	13	2	299	NA	96	13	NA	NA	NA	8 (S:4, C:2, 0:2)	
	Fang et al ⁴¹ Malham et al ⁴³	2018 2019	Retrospective Retrospective	4 3741	0-6 <18	1.2 [¶] 14.0	NA NA	NA	NA 117.6	NA NA	NA NA	NA NA	NA 39	NA 2.50 (1.80-3.40)	NA 12	NA 6	0 3	0 2	NA NA	5 (S:2, C:0, 0:3) 8 (S:4, C:2, 0:2)	
	Olén et al ^{61,‡‡‡}	2019	Retrospective	1918	<18	NA	NA	NA	NA	NA	NA	NA	NA	2.50 (1.80-5.40) NA	16	NA	NA	2 NA	NA	8 (S:4, C:2, 0:2) 8 (S:4, C:2, 0:2)	
IBD (no distinction made between	Markowitz et al ⁶²	1993	Retrospective	165	NA	11.4	15.0****	-	NA	NA	NA	NA	0****	NA	0 ⁺⁺⁺⁺	0++++		0++++	0 ⁺⁺⁺⁺	1 (S:1, C:0, 0:0)	
CD or UC)	Lee et al ⁶³ Chouliaras	2005 2010	Retrospective Retrospective	112 31	5-21 [§] NA	NA 8.7	NA NA	- NA	35.0 NA	NA NA	NA NA	100 NA	0 1	NA NA	0 0	0 1	0 0	0 1	0 0	3 (S:1, C:0, 0:2) 3 (S:1, C:0, 0:2)	
	et al ⁶⁴														-		-		-	. (,, 0.2)	

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Tat	ole III.	Conti	nued																			
					Patient		Age at diagnosis or		Age at diagnosis of	Follow-up		comita cations		Numbers of patients wit		Numbers of				nts with Icer (n)		
Diseas	ses	Author	Year (reference*)	Study design	numbers (n)	Age at diagnosis (y)	onset (y,	Age at study (y, mean)	cancers (y, median) [†]	duration			Anti- TNFα	overall	cancers	patients with CRC	Overall	HL	NHL	Leukemia	Newcastle- Ottawa scale [‡]	Jadad score
	Co	olletti et al ⁶⁵	2013	Retrospective	4343	≤18	NA	NA	NA	NA	NA	NA	NA	7	Anti-TNFα exposed: 4.77 (1.56-14.61); Non biologic therapies: 5.09 (1.35-19.15)	0	4	1	0	1	5 (S:2, C:2, 0:1)	NA
	El- et	-Matary al ⁶⁶	2020	Retrospective	947	<18	14.0	NA	NA	NA	NA	NA	NA	17	NA	NA	NA	NA	NA	NA	6 (S:4, C:0, 0:2)	NA

AZA, azathioprine; C, comparability; HL, Hodgkin's lymphoma; NA, not available; NHL, non-Hodgkin's lymphoma; O, outcome; S, selection.

*See supplementary reference list.

†NA indicates data regarding age of cancer diagnosis is not available and "-" indicates no reported case of cancer.

‡Newcastle-Ottawa scale, total score (S, selection (0-4); C, Comparability (0-2); O, Outcome (0-3)).

§Data as the definition of age at study.

Mean or median ages of patients with CD and UC (Gold 1993, Kelsen 2011, Peneau 2013, Fang 2018).

**Follow-up duration from the patients who completed the trial (Markowitz 2000).

ttMean ages at start of IFX (Hyams 2009, Sinitsky 2010, Kelsen 2011).

##Two patients who were over 21 years old were included (Ashworth 2012).

§§Mean age was calculated from each medium data of step-wise age (Skyring 1965, Michener 1979).

¶¶Mean follow-up duration of 124 patients (Hyams 2012).

****Patients were defined as "children".

+++Data as IBDs (Hyams 2017).

###Data were from cohort of Denmark. The cohort of Sweden in this study were duplicate with that of Olén 2017.

§§§Mean ages at admission (Holowach 1956).

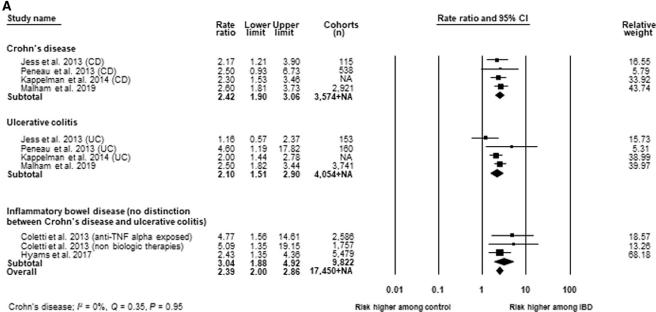
¶¶¶Mean follow-up duration of 333 patients (Michener 1979).

*****Mean ages at start of immunosuppressive (Markowitz 1993).

ttttData were quoted from the study by Kirschner et al (Markowitz 1993).

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Crohn's disease; P = 0%, Q = 0.35, P = 0.95 Ulcerative colitis; P = 41.54%, Q = 5.13, P = 0.16

Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); P = 0%, Q = 1.77, P = 0.41 Overall; P = 0%, Q = 9.02, P = 0.53

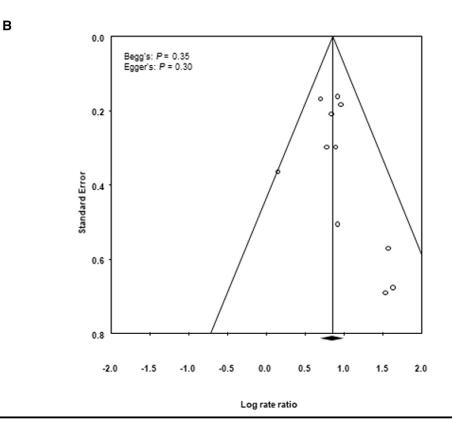


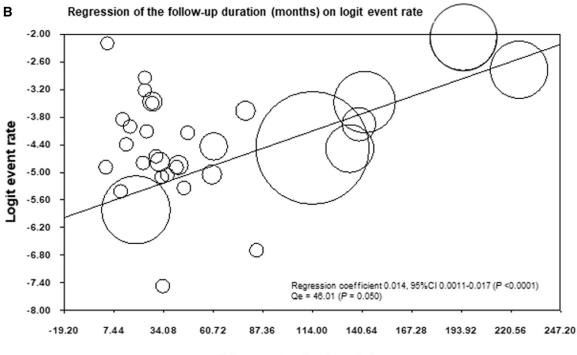
Figure 2. Meta-analysis of the risk of overall cancers reported as SIR among patients with pediatric IBD. A, Forest plot of the risk of overall cancers reported as SIR among patients with pediatric IBD. B, Funnel plot of the studies included in Figure 2, A.

ORIGINAL ARTICLES

Α	Study name_					Event rate and 95% C	1
Cr	ohn's disease	Event rate	Lower limit	Upper limit	Total		Relative weight
Su	Weedon et al. 1973 Postuma et al. 1985 Verhave et al. 1990 Gold et al. 1993 Gryboski et al. 1994 Langholz et al. 2090 Stephens et al. 2000 Stephens et al. 2000 General et al. 2003 de Ridder et al. 2004 Hyams et al. 2009 Jakobsen et al. 2009 Jakobsen et al. 2009 Jakobsen et al. 2009 Viola et al. 2009 Viola et al. 2009 Viola et al. 2009 Viola et al. 2010 Grombe et al. 2010 Grombe et al. 2011 Hyams et al. 2011 Kierkus et al. 2011 Kierkus et al. 2012 Assa et al. 2012 Assa et al. 2013 Navas-Lopez et al. 2013 Navas-Lopez et al. 2014 Vahabmezhad et al. 2014 Hyams et al. 2017 Malet et al. 2017 Choi et al. 2017 Malham et al. 2019 bitotal	0.027 0.030 0.031 0.025 0.021 0.0089 0.0089 0.0044 0.0044 0.0012 0.0050 0.050 0.050 0.050 0.052 0.052 0.052 0.052 0.055 0.0025 0.0050 0.0055 0	0.015 0.0043 0.0024 0.0035 0.0019 0.0035 0.00038 0.00028 0.00028 0.00028 0.00028 0.00028 0.00028 0.00028 0.00028 0.00011 0.00011 0.00011 0.00011 0.00015 0.00015 0.00015 0.00015 0.00015 0.00015 0.00015 0.00015 0.00015 0.00015 0.00017 0.00015 0.00017 0.0000000000	0.046 0.19 0.405 0.283 0.0891 0.0891 0.0019938 0.00000000000000000000000000000000000	12 / 449 1 / 33 0 / 12 0 / 15 1 / 40 0 / 23 0 / 82 0 / 82 0 / 404 0 / 19 0 / 404 0 / 19 0 / 100 0		5273 1.790 12.78 1.882 1.882 1.882 1.882 1.882 1.1852 1.18
U	cerative colitis						
Su	Ladd et al. 1935 Korrelitz et al. 1962 Skyring et al. 1985 Devroede et al. 1971 Michener et al. 1971 Michener et al. 1979 Verhave et al. 1999 Langhoz et al. 2099 Hyams et al. 2010 Kelsen et al. 2011 Jess et al. 2013 Peneau et al. 2013 Vahobnezhad et al. 2014 Hyams et al. 2017 Olen et al. 2019 Malham et al. 2019	0.039 0.037 0.047 0.0350 0.0350 0.0350 0.0359 0.0559 0.00559 0.00559 0.00559 0.00559 0.00559 0.00559 0.00559 0.00559 0.00559 0.00559 0.00559 0.00559 0.00559 0.00559 0.00559 0.00559 0.00559 0.00559 0.00559	0.0054 0.012 0.010 0.016 8.8880 0.0018 0.00089 0.0031 0.00091 0.0058 0.0058 0.0058 0.0058 0.0058 0.0058 0.0058	0.23 0.11 0.17 0.055 0.48 0.48 0.48 0.48 0.48 0.48 0.48 0.48	1 / 28 9 / 880 52 / 338 10 / 333 0 / 4 2 / 150 0 / 52 2 / 338 0 / 4 1 / 80 0 / 52 0 / 4 2 / 150 0 / 52 0 / 4 2 / 150 0 / 52 0 / 4 3 / 150 0 / 1.432 259 / 4.648 39 / 3.741 435 / 11.557	+++++++++++++++++++++++++++++++++++++	8740745020000000000000000 874074502000000000000000 97407450200000000000000000000000000000000
	flammatory bowel disease (no distinction						
Su	tween Crohn's disease and ulcerative colitis) Markowitz_et al. 1993 Lee et al. 2005 Choularas et al. 2010 Colletti et al. 2013 El-Matary et al. 2020 bitotal verall	0.0030 0.0842 0.0016 0.018 0.0068 0.018	0.00019 0.00028 0.0045 0.0017 0.011 0.0015 0.013	0.046 0.067 0.030 0.029 0.030 0.030 0.025	0 / 165 0 / 112 1 / 31 7 / 4,343 17 / 947 25 / 5,568 700 / 32,417		14.28 14.25 25.91 26.88
						0.00 0.50 1	00
					Pooled ra	ates of overall malignancies	in patients of IBD
Cra Ulc	erogeneity hn's disease; μ = 78.90%, Q = 180.07, P <0.0001 erative colitis; μ = 91.59%, Q = 213.98, P <0.0001 ammatory bowel disease (no distinction between C crall; μ = 91.0%, Q = 582.98, P <0.0001	rohn's diseas	e and ulcerative	e colitis); P = 8	7.31%, Q = 31.51, F	² <0.0001	

Overall; P = 89.10%, Q = 568.96, P <0.0001

Figure 3. Meta-analysis of incidence rates of overall cancers among pediatric IBD. **A**, Forest plot of incidence rates of overall cancers among pediatric IBD. **B**, Meta-regression of the follow-up duration (*months*) and the risk of overall cancers. **C**, Funnel plot of the studies included in Figure 3, A.



Follow-up duration (months)

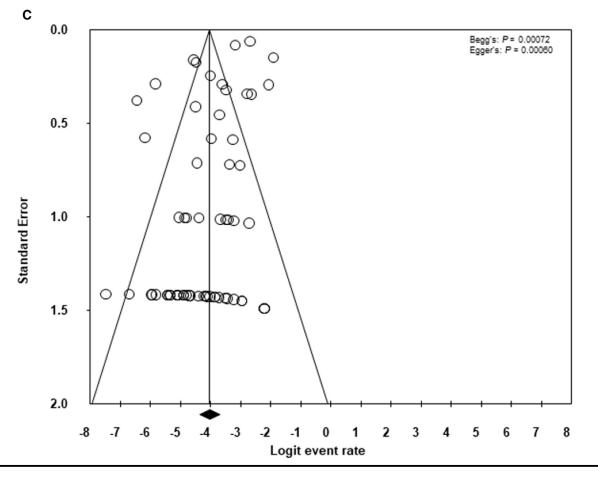
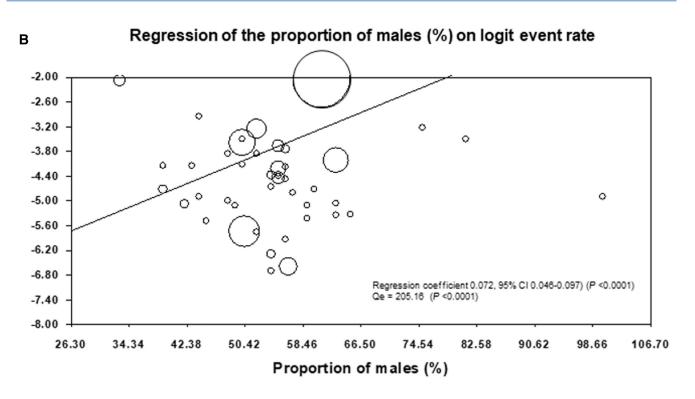


Figure 3. (continued)

ORIGINAL ARTICLES

A <u>Study name</u>	Event rate	Lower limit	Upper limit	Total	Event rate and 95% CI	Relative weight
Crohn's disease						neight
Weedon et al. 1973 Postuma et al. 1985 Verhave et al. 1990 Gold et al. 1990 Gold et al. 1994 Gryboski et al. 1994 Langholz et al. 2094 Markowizz et al. 2000 Stephens et al. 2000 Stephens et al. 2007 de Ridder et al. 2008 Vernier-Massouille, et al. 2008 Duncova et al. 2009 Hyams et al. 2009 Hyams et al. 2009 Hyams et al. 2009 Pigneur et al. 2009 Viola et al. 2009 Pigneur et al. 2010 Crombe et al. 2010 Crombe et al. 2011 Keisen et al. 2011 Keisen et al. 2012 Hyams et al. 2011 Keisen et al. 2012 Hyams et al. 2012 Hyams et al. 2012 Hyams et al. 2012 Hyams et al. 2014 Rosh et al. 2014 Rosh et al. 2017 Mallet et al. 2017 Mallet et al. 2018 Turner et al. 2018 Jurner et al. 2019 Olen et al. 2019 Olen et al. 2019 Olen et al. 2019 Olen et al. 2019 Subtotal	0.018 0.031 0.035 0.021 8.0089 0.021 8.0089 0.021 8.0095 0.0055 0.0055 0.0055 0.0055 0.0029 8.0029 0.0055 0.0029 0.00029 0	0.0029 0.00191 0.0019 0.00176 0.00178 0.00178 0.00178 0.00178 0.00178 0.00178 0.00015 0.00031 0.00017 0.00015 0.000100000000	0.035 0.200 0.0917 0.2139 0.0017 0.00119 0.00019 0.00119 0.00019 0.00019 0.0000000000	8/449 0/15 4/140 0/23 0/15 0/23 0/23 0/23 0/23 0/23 0/23 0/23 0/206 0/20000000000		6.88 189 17,796 1.880233 1.88023 1.8803 1.8803 1.88033 1.88033 1.88033 1.8
Ulcerative colitis						
Ladd et al. 1935 Lagercrantz et al. 1955 Holowach et al. 1956 Michener et al. 1961 Hijmans et al. 1962 Korelitz et al. 1962 Skyring et al. 1965 Patterson et al. 1973 Michener et al. 1979 Verhave et al. 1990 Ahsgren et al. 1993 Gold et al. 1993 Hyams et al. 1998 Langholz et al. 1997 Falcone et al. 2000 Gower-Rousseau et al. 2009 Jakobsen et al. 2009 Hyams et al. 2010 Kelsen et al. 2011 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017 Olén et al. 2019 Olén et al. 2020 Subtotal	0.038 0.044 0.11 0.011 0.037 0.025 0.023 0.011 0.027 0.050 0.015 0.10 0.012 0.013 0.013 0.0088 0.0088 0.0033 0.0094 0.10 0.0083 0.0094 0.10 0.0083 0.016 0.00035 0.021 0.0083 0.020	0.0054 0.020 0.028 0.087 0.00071 0.018 0.0083 0.00089 0.014 0.0031 0.00094 0.0019 0.0019 0.0019 0.0019 0.0012 0.0012 0.0012 0.0012 0.00059 0.00059 0.00059 0.00059 0.00059 0.00059 0.00059 0.00059 0.00059 0.00059 0.00059 0.00059 0.00059 0.00059 0.00059 0.00059 0.0010 0.0010 0.0010 0.0011 0.0012	0.23 0.094 0.15 0.15 0.087 0.094 0.15 0.051 0.48 0.061 0.083 0.099 0.083 0.099 0.083 0.099 0.083 0.099 0.083 0.099 0.080 0.12 0.13 0.67 0.043 0.025 0.0056 0.025 0.0056 0.014 0.034	1/28 8/137 2/18 48/401 0/43 5/134 2/80 1/43 0/44 9/333 0/9 0/32 0/4 2/171 1/80 0/73 1/113 2/60 0/52 0/4 1/160 0/31 0/1,432 98/4,648 12/3,741 16/1,918 203/13,787		3,45 5,535 8,18 2,440 4,47 2,538 2,440 2,447 2,538 2,447 2,447 2,447 2,447 2,447 2,449 2,450 2,500 2,5
between Crohn's disease and ulcerative colitis) Markowitz et al. 1993		0.00019	0.048	0 / 185		25.03
Lee et al. 2005	0.0030 0.0044	0.00019 0.00028	0.046 0.067	0 / 165 0 / 112		25.03
Chouliaras et al. 2010	0.016	0.0010	0.21	0/31		24.89
Colletti et al. 2013 Subtotal	0.00012 0.0022	0.0000072 0.00030	0.0018 0.017	0 / 4,343 0 / 4,651	7	25.07
Overall	0.010	0.0074	0.014	244 / 35,083	P	
					0.00 0.50 1.00	
Heterogeneity				Pooled rate	es of colorectal cancer in patien	ts of IBD
Crohn's disease; μ = 41.30%, Q = 66.44, P = 0.0040 Ulcerative colitis; μ = 87.95%, Q = 207.48, P <0.000 Inflammatory bowel disease (studies that did not diff Overall; μ = 81.30%, Q = 341.54, P <0.0001	1	en Crohn's disea	ase and ulcera	ative colitis); P = 54.	.34%, Q = 6.57, P = 0.087	

Figure 5. Meta-analysis of incidence rates of CRC among pediatric IBD. **A**, Forest plot of incidence rates of CRC among pediatric IBD. **B**, Meta-regression of the proportion of male (%) and the risk of CRC. **C**, Meta-regression of the age at diagnosis (*year*) and the risk of CRC. **D**, Funnel plot of the studies included in Figure 5, A.



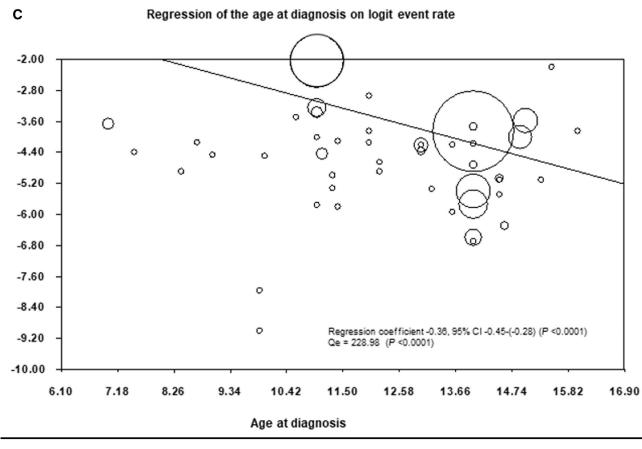


Figure 5. (continued)

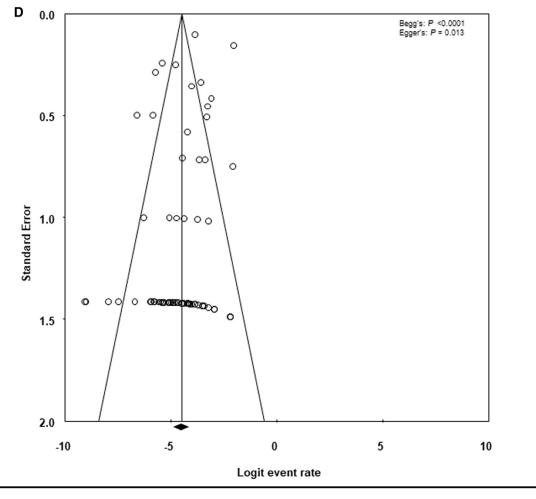


Figure 5. (continued)

Meta-Analysis of Incidence Rates of Colorectal Cancer in Pediatric IBD

There were only 2 pediatric IBD (no distinction between CD and UC) studies and 1 pediatric UC study reporting the SIR of CRC, therefore, meta-analysis by SIR was not possible. The pooled incidence rate of CRC was performed from 9 prospective and 52 retrospective studies (1 study included both study designs) with a total of 35 083 patients with pediatric IBD.

As shown in Figure 5, A, the pooled incidence rate of CRC in CD was 0.0075 (95% CI 0.0049-0.011) with moderate heterogeneity ($I^2 = 41.30\%$). The pooled incidence rate of CRC in UC was 0.020 (95% CI 0.012-0.034) with high heterogeneity ($I^2 = 87.95\%$). When including all patients with pediatric IBD, the pooled incidence rate was 0.010 (95% CI 0.0074-0.014) with high heterogeneity $(I^2 = 81.30\%)$ (Figure 5, A). Meta-regression showed that there was a positive correlation between the proportion of male patients and the risk of CRC (regression coefficient 0.072, 95% CI 0.046-0.097, P <.0001) (Figure 5, B), suggestive of higher risk in male patients, and a negative correlation between the age at diagnosis or onset and the risk of CRC (regression coefficient -0.36, 95% CI -0.45 to

-0.28, P < .0001) (Figure 5, C), suggestive of higher risk in patients with early onset disease. Analyses of variance showed that both Qe were statistically significant (Qe = 205.16, 228.98, P < .0001, < .0001, respectively),indicating that heterogeneity could not be explained only by each factor. According to meta-regression analyses, the risk of CRC development was not particularly affected by the history of concomitant medications such as steroid, immunomodulator and anti-TNF agents (Tables V-VII). Visual inspection of the funnel plot did not show asymmetry, but there were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, = 0.013, respectively; Figure 5, D). Funnel plots of the studies reporting the risk of CRC among patients with CD and UC were also shown in Figure 6, A, D, respectively (available at www.jpeds.com).

Meta-Analysis of Incidence Rates of Hematologic Cancers in Pediatric IBD

There was only 1 study that reported the SIR of hematologic cancers in patients with pediatric IBD, therefore, metaanalysis by SIR was not possible. The pooled incidence rates of hematologic cancers were assessed from 9 prospective and 40 retrospective studies (1 study included both study designs) with a total of 31 477 patients with pediatric IBD.

As shown in **Figure 7**, A (available at www.jpeds.com), the pooled incidence rate of hematologic cancers in patients with CD and patients with UC were 0.0061 (95% CI 0.0040-0.0090) and 0.0045 (95% CI 0.0026-0.0079), respectively with low heterogeneities ($I^2 = 27.14\%$, 31.66%, respectively). When all patients with pediatric IBD were included, the pooled incidence rate was 0.0054 (95% CI 0.0039-0.0075) with moderate heterogeneity ($I^2 = 34.25\%$). Visual inspection of the funnel plot did not show asymmetry, but there were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, < .0001, respectively; **Figure 7**, B).

When individual hematologic cancers were analyzed separately, the pooled incidence rates of Hodgkin's lymphoma in all patients with pediatric IBD was 0.0061 (95% CI 0.0040-0.0093) with low heterogeneity ($I^2 = 36.77\%$) (Figure 8, A; available at www.jpeds.com). The pooled incidence rates of non-Hodgkin's lymphoma in all patients with IBD was 0.0065 (95% CI 0.0041-0.010) with moderate heterogeneity $(I^2 = 41.90\%)$ (Figure 9, A; available at www.jpeds.com). The pooled rates of leukemia in all patients with IBD was 0.0056 (95% CI 0.0028-0.011) with low heterogeneity $(I^2 = 24.20\%)$ (Figure 10, A; available at www.jpeds.com). According to meta-regression analyses, the risk of hematologic cancers development including Hodgkin's lymphoma, non-Hodgkin's lymphoma, and leukemia was not particularly affected by the history of concomitant medications such as steroid, immunomodulatory, and anti-TNF agents (Tables V-VII).

Temporal Trend of Cancer Incidence Assessed by Cumulative Meta-Analysis

Cumulative meta-analyses of each outcomes ranked by year were performed and shown in Figure 9, A-G. The number of studies included for overall risk of cancers reported as SIR were small and were all published after 2013, so no temporal trend could be assessed (Figure 11, A; available at www.jpeds.com). For the incidence of colorectal and hematologic cancers, we investigated the temporal change of the risk of each type of cancer by assessing the correlation coefficient of each cumulative meta-analysis. We found that as the reporting years became more recent, the incidence of cancer were significantly reduced in all meta-analyses (overall CRC, cumulative cancer, hematologic cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and leukemia) for CD and UC (Figure 11, B-G). Regression coefficients for cumulative meta-analyses among patients with IBD about overall cancer, CRC, and hematologic cancer were 0.019, 0.0049, and 0.0018, respectively (95% CI 0.018-0.021 [P < .0001], 0.0043-0.0054 [P <.0001], and 0.0017-0.0019 [P <.0001], respectively).

Sensitivity Analyses

We performed influence analyses by removing individual studies from the meta-analyses to assess the influence of any particular study on the results (Figure 12, A-G; available at www.jpeds.com). This demonstrated that the random effects estimate was not greatly influenced by any particular study.

We also undertook meta-analyses excluding studies with less than 30 patients when possible. Each analysis showed similar results compared with the aforementioned results (data not shown).

Discussion

We performed a systematic review and meta-analysis and demonstrated that patients with IBD diagnosed in childhood have a significantly increased risk of cancer when compared with the general population. In addition, we comprehensively analyzed incidence rates of CRC and hematologic cancers, and demonstrated that the incidence of these cancers appeared to be down-trending, which have not been referred in the previous systematic review.⁷

Nearly 10% of newly diagnosed patients with CD or UC are below 15 years of age^{27,28}; therefore, understanding the risk of cancer development in the pediatric population is essential in the accurate evaluation and management of patients with pediatric IBD. Our meta-analysis demonstrated that patients with pediatric CD have a 2.42-fold increased risk of cancers and patients with UC have a 2.10-fold increased risk when compared with a general pediatric population. Interpreting the SIR, however, is strengthened when evaluated with a corresponding incidence rate. Thus, we also assessed the pooled incidence rates of the risk of overall cancer and cancer subtypes among patients with pediatric IBD. The incidence rate of overall cancer in CD and UC was 0.014 and 0.031, respectively. For comparative purposes, within the surveillance, epidemiology, and end result (SEER) database, the incidence rate of cancer among children and adolescents were 0.00014 (ages 10-14 years), 0.00022 (ages 15-19 years), and 0.00036 (ages 20-24 years), respectively.²⁹

In a population-based study, Ekbom et al reported that children who develop UC before 14 years of age had a cumulative CRC incidence rate of 5% at 20 years and 40% at 35 years.³⁰ In our analysis, the incidence rate of CRC among pediatric patients with UC was 0.020. When compared with UC, pediatric patients with CD had a numerically lower incidence of CRC (0.0075). Meta-regression in UC demonstrated an increased risk of CRC development in male patients and with younger disease onset. The annual incidence of CRC within the SEER database (age-adjusted rate, 2007-2011) is 0.000010 for adolescents (ages 20-24 years) and 0.0022 for adults over age 65 years.²⁹

Over the past decade, immunosuppressive agents as well as biologic agents, are increasingly used to treat pediatric IBD.^{31,32} However, the risks of therapies need to be considered as evidence suggests that in particular, thiopurines,

when used alone or in combination with anti-TNF α therapies, increase the risk of lymphoma.³³ In our analysis, the incidence rates of Hodgkin's lymphoma, non-Hodgkin's lymphoma, and leukemia in pediatric CD and UC were greater than any age group of the general population within the SEER database (age-adjusted rate, 2007-2011).²⁹ The risk of cancers in patients exposed to thiopurines and anti-TNF agents remain controversial.^{34,35} In our study, we did not find a correlation between thiopurine or anti-TNF α agent use and the risk of any cancers (Tables V-VII); this may have been due to the inclusion of several research articles with short follow-up periods. Indeed, there have been reports of lymphoma and non-melanoma skin cancer risk associated with thiopurine use which referred that patients using thiopurines seem to have an increased risk of lymphoma or non-melanoma skin cancer that is proportional to therapy duration.^{34,36} Although not statistically significant, there was a trend of correlation between thiopurine use and the risk of lymphoma (Table VI). Recently, it has also been reported that hepatosplenic T-cell lymphoma is a rare but concerning issue in young adult male patients with IBD who have been exposed to thiopurines, however, there was not enough data to analyze this risk in our meta-analysis.

The results of cumulative analyses showed that the incidence of cancers appear to be down-trending in patients with pediatric IBD. This is in concordance with studies reporting a decreased risk of CRC incidence in adult IBD population.³⁷ The decrease in the risk of CRC over time may be owing to the changes in treatment of IBD.³⁸ However, our study found a down-trending risk of overall and hematologic cancers. This phenomenon may not be obvious in other autoimmune diseases treated with similar medications: the average lymphoma risk in recently diagnosed patients with rheumatoid arthritis is similar in magnitude to that reported in historical cohorts.³⁹ In addition, we could not investigate whether patients with very early onset IBD carry a higher risk of cancer because there was only one study which referred to this patient population.⁴⁰

Our study has some limitations. At first, after we identified 969 127 records through database, 968 806 of records were excluded after initial screening of titles and abstracts. Papers not related to the outcome of our study, or duplicate papers in the databases were deleted at this stage. However, the number of duplicate papers cannot be accurately assessed: as mentioned in our study, only the first 1000 articles were technically available for review in each search for Google Scholar. Second, our analyses with patients with pediatric IBD mainly included retrospective observational studies. In addition, 16 studies (24.24%) included adolescent-onset patients with IBD with childhood-onset patients, though each average age of 12 years studies was below 15 years old. The remaining 4 studies did not mention the average age of onset of disease but have exclusively included patients with childhood-onset IBD. Moreover, the qualities of the observational studies were modest based on the Newcastle-Ottawa scale. Though overall quality of each assessment among this systematic review was low, it seems to be due to the fact that the quality of the observational studies included was modest, as we referred above. Most of the studies, which were included in our analyses, described the occurrence of cancers among patients with IBD diagnosed in childhood, but all cancers might not occur during the childhood period. Therefore, we were not able to simply compare the event rates of our analyses with the existing age-adjusted rates of SEER database. Besides, the incidence rate findings of our meta-analyses were compared with the SEER database, but a formal statistical analysis could not be undertaken. Skin cancer and other solid cancers could not be analyzed because there were no reports among patients with pediatric IBD. Our review could not assess the influence of various treatment on the risk of cancers. Aardoom et al reported cancer risk in patients with childhood-onset IBD separately as fatal and nonfatal, however, it was unclear whether treatments were significantly involved in the onset of cancer.7 We conducted metaregressions with factors such as concomitant steroids, anti-TNF agents, or immunomodulator use, and found that none of these drugs was significantly associated with the occurrence of cancer. These findings are in concordance with a previous study that reported that disease activity of rheumatologic diseases among adults are involved in the subsequent development of cancer.⁴¹ In particular, there was no evidence of an association between anti-TNF agent use and cancer risk among patients with rheumatological diseases. It may be conceivable that improved disease control with newer, more effective therapeutic agents will help mitigate the increased risk of cancer associated with pediatric rheumatologic diseases. The duration of immunomodulators use may influence the incidence of malignancy, however, because of the lack of papers describing the duration of anti-TNF agents and immunomodulators use, we could not account for duration of treatment with these medications in our analyses. In addition, we could not investigate the correlation of the development of malignancy between races: in a recent report, it was referred that there may be differences in the risk of lymphoma due to immunomodulators use between races.⁴² There was some baseline variability in patient population among the different studies: for instance, some of the papers included in our analyses were on treatment-biased patients with IBD. This variability may also contribute to the heterogeneity that was seen in a small number of our analyses. Indeed, we undertook meta-regression with factors such as age of diagnosis, duration of follow-up period, and proportion of males for each analysis and found that there were correlations with some of our results. Our study presented the decrease in incidence of malignancies over time with analyzing cumulative meta-analyses. However, without detailed individual patient data, it may be difficult to confirm that the incidence of newly developed cancers is actually decreasing. We found small study effects (publication biases) among some of our metaanalyses, though visual inspection of the funnel plots showed no asymmetry. Some smaller studies may be more likely to be published when they have significant results, which in turn biases the results of a meta-analysis.⁴³ We performed metaanalyses including or excluding studies with less than 30 patients when possible, but results were similar. We were unable to perform sensitivity analyses limited to population-based studies to avoid referral biases. Only 11 out of 66 papers were population-based studies in our analyses, and the numbers were even smaller for individual cancers. Instead, we conducted influence analyses as one of the sensitivity analyses to identify the influential papers. We demonstrated that the random effects estimate was not greatly influenced by any particular study.

In conclusion, this systematic review and meta-analysis showed that patients with IBD diagnosed in childhood have an increased risk of cancers when compared with the general population. This risk appeared to be attributed mostly to the development of CRC and hematologic cancers with risk factors that included patient sex (male) as well as younger onset and longer duration of disease, but not thiopurine or anti-TNF agent use. We also observed that the risk of these cancers appeared to be down-trending over time. ■

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50 Years Ago in The JOURNAL OF PEDIATRICS

Diagnosis of Coagulation Defects in Reye Syndrome

Schwartz A. The coagulation defect in Reye's syndrome. J Pediatr 1971;78:326-8.

Fifty years ago in *The Journal*, Schwartz described a child with Reye syndrome, likely from a myxovirus, admitted to Yale-New Haven Hospital with sudden hemorrhagic diathesis. This child had prolonged prothrombin time and partial thromboplastin time and generally low levels of coagulation factors. Although the low levels of coagulation factors was suggestive of disseminated intravascular coagulation (DIC), the normal levels of factor VIII, normal platelet count, and absence of fibrin split products clinched the correct diagnosis of hepatic failure, allowing for appropriate therapy. Schwartz cautioned about the potentially deleterious effect of an incorrect diagnosis of DIC, which was heparin therapy in a bleeding child.

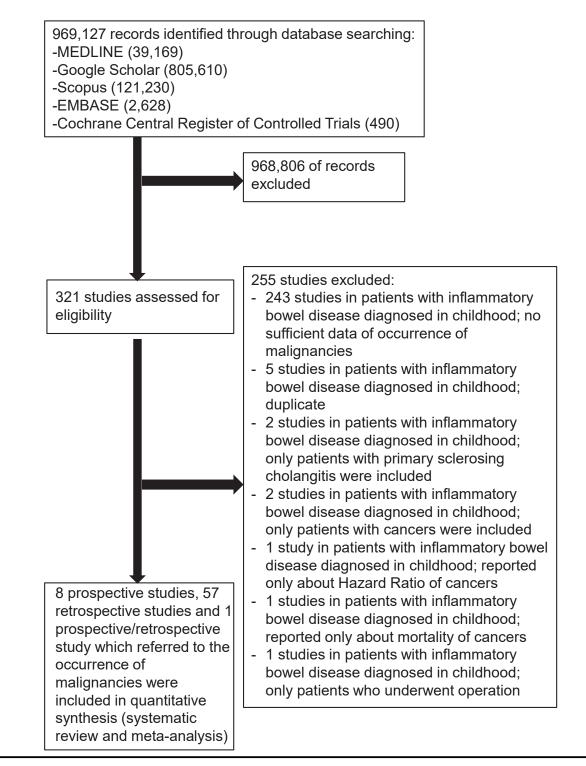
The world is currently in the midst of the COVID-19 pandemic. The multisystem inflammatory syndrome in children (MIS-C) is thought to be a manifestation of COVID-19, which is caused by a coronavirus. In contrast to Reye syndrome, thrombosis is a major concern in MIS-C. Bleeding is not common with MIS-C, but these children tend to have prolonged prothrombin time, low platelet count, and elevated levels of D-dimer, a fibrin split product.¹ A large proportion of these children receive heparin therapy to prevent thrombosis. At Yale-New Haven Children's Hospital and other children's hospital in the US, viscoelastic testing of coagulation with thromboelastography or thromboelastometry is now available. Reports in adults with COVID-19 suggest a prothrombotic profile using these tests. Studies to characterize the coagulation profile using viscoelastic testing in children with MIS-C are ongoing.

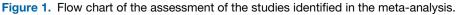
For the past 50 years, prothrombin time, partial thromboplastin time and platelet count have been the first-line workup for children with probable defects in hemostasis. Novel tests, such as viscoelastic testing, are now able to assess the combined effect of coagulation factors and platelets. Increasing experience with the use of these test may provide further insight into defects in hemostasis in other virus-related syndromes. Although heparin has been abandoned as a therapy for DIC, viscoelastic testing also may be used to titrate heparin to avoid its deleterious effect of bleeding.

Anjali Gupta, MD E. Vincent S. Faustino, MD, MHS Department of Pediatrics Critical Care Medicine Yale School of Medicine New Haven, Connecticut

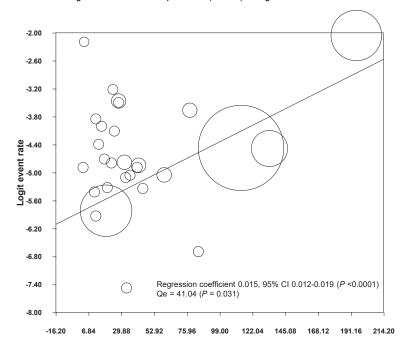
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Follow-up duration (months)

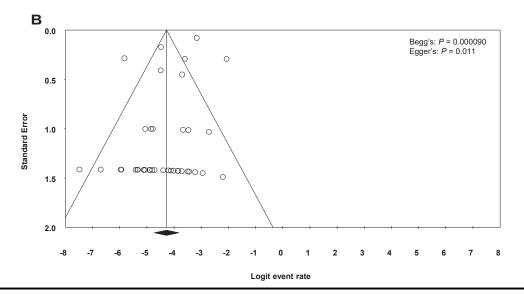


Figure 4. A, Meta-regression of the follow-up duration (*months*) and the risk of overall cancers among patients with CD. Metaregression showed that there was a positive correlation between the follow-up duration of the studies and the risk of overall cancers (regression coefficient 0.015, 95% CI 0.012-0.019, P < .0001). ANOVA showed that Qe was statistically significant (Qe = 41.04, P = .031), indicating that heterogeneity could not be explained only by this factor. **B**, Funnel plot of the studies reporting the risk of overall cancers among patients with CD included in **Figure 3**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P = .000090, .011, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **C**, Meta-regression of the follow-up duration (months) and the risk of overall cancers among patients with UC. Meta-regression showed that there was a positive correlation between the follow-up duration of the studies and the risk of overall cancers (regression coefficient 0.014, 95% CI 0.0091-0.019, P < .0001). ANOVA showed that Qe was not statistically significant (Qe = 10.59, P = .16), indicating that heterogeneity was largely explained by this factor and that there remains no statistically significant heterogeneity once follow-up duration has been taken into consideration. **D**, Funnel plot of the studies reporting the risk of overall cancers among patients with UC included in **Figure 3**, A. There were no small-study effects or publication biases as assessed by the Begg and Egger test (P = .51, .16, respectively). **E**, Funnel plot of the studies reporting the risk of overall cancers among patients with IBD (studies that did not differentiate between CD and UC) included in **Figure 3**, A. There were no small-study effects or publication biases as assessed by the Begg and Egger tests (P = .81, .71, respectively).

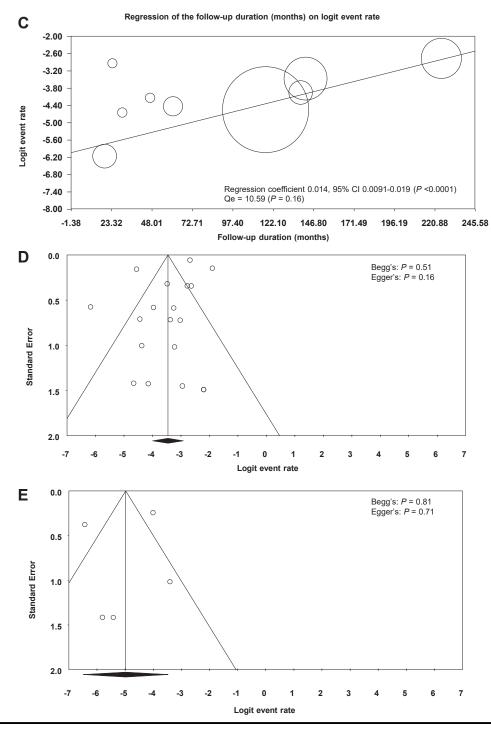


Figure 4. (continued)

Komaki et al

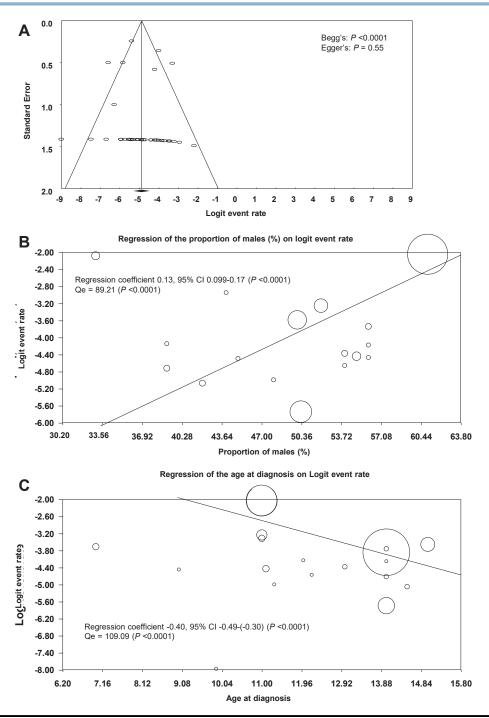


Figure 6. A, Funnel plot of the studies reporting the risk of CRC among patients with CD included in **Figure 5**, A. There were small-study effects or publication biases as assessed by the Begg test but not by the Egger tests (P < .0001, = .55, respectively). Visual inspection of the funnel plot appeared to show no asymmetry. **B**, Meta-regression of the proportion of male patients (%) and the risk of CRC among patients with UC. Meta-regression showed that there was a positive correlation between the proportion of male patients and the risk of CRC (regression coefficient 0.13, 95% CI 0.099-0.17, P < .0001). ANOVA showed that Qe was statistically significant (Qe = 89.21, P < .0001), indicating that heterogeneity could not be explained only by this factor. **C**, Meta-regression of age at diagnosis or onset (*year*), and the risk of CRC among patients with UC. Meta-regression showed that there was a negative correlation between age at diagnosis or onset, and the risk of CRC (regression coefficient -0.40, 95% CI -0.49 to -0.30, P < .0001). ANOVA showed that Qe was statistically significant (Qe = 109.09, P < .0001), indicating that heterogeneity could not be explained only by this factor. **D**, Funnel plot of the studies reporting the risk of CRC among patients with UC included in **Figure 5**, A. There were no small-study effects or publication biases as assessed by the Begg and Egger tests (P = .19, .48, respectively). **E**, Funnel plot of the studies reporting the risk of CRC among patients with IBD (studies that did not differentiate between CD and UC) included in **Figure 5**, A. There were no small-study effects or publication biases as assessed by the Begg and Egger tests (P = .089, .20, respectively).

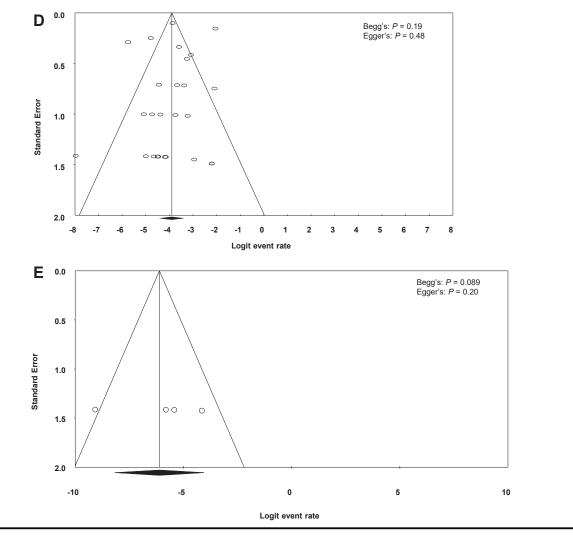


Figure 6. (Continued)

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	0.0012 0.0068 0.0078 0.050 0.021 0.022 0.0042 0.0042 0.0042 0.0043 0.0048 0.0027 0.0049 0.0019 0.0019 0.0026 0.0019 0.0026 0.0018 0.0017 0.0027 0.0026 0.0015 0.0027 0.0027 0.0021 0.0021 0.0051 0.0051 0.0061 0.0051 0.0062 0.0051 0.0062 0.0051 0.0062 0.0051 0.0062 0.0051 0.0062 0.0051 0.0062 0.0051 0.0062 0.0051 0.0062 0.0051 0.0062 0.0051 0.0062 0.0051 0.0062 0.0051 0.0062 0.0051 0.0062 0.0051 0.0062 0.0051 0.0062 0.0051 0.0062 0.0050 0.0051 0.0051 0.0051 0.0051 0.0051 0.0051 0.0051 0.0051 0.0051 0.0051 0.0051 0.0051 0.0051 0.0051 0.0051 0.0051 0.0052 0.0052 0.0052 0.0052 0.0054 0.0054 0.0054 0.0050 0.0052 0.0054 0.0054 0.0054 0.0054 0.0050 0.0054 0.0054 0.0055 0.0054 0.0055 0.0054 0.0055 0.0054 0.0055 0	0.0012 0.00077 0.0060 0.00038 0.0078 0.00111 0.050 0.0031 0.012 0.00076 0.029 0.0018 0.0041 0.0026 0.0041 0.0027 0.0041 0.0027 0.0042 0.0018 0.0043 0.00017 0.0044 0.00330 0.0048 0.00031 0.0049 0.00030 0.0048 0.00276 0.0049 0.00030 0.0048 0.00266 0.0049 0.00266 0.0026 0.00116 0.0027 0.00116 0.0026 0.0011 0.0017 0.00289 0.0021 0.000291 0.0022 0.0011 0.0017 0.00292 0.0021 0.00291 0.0021 0.00292 0.0021 0.00291 0.0021 0.00292 0.00201 0.00292	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	0.0078 0.0011 0.053 1/128 0.050 0.0031 0.48 0/9 0.021 0.00076 0.17 0/40 0.0221 0.0018 0.34 0/16 0.0229 0.0018 0.34 0/16 0.0229 0.0018 0.23 0/16 0.0231 0.0026 0.023 0/17 0.0243 0.00051 0.12 0/600 0.0243 0.00017 0.011 0/188 0.0027 0.00017 0.011 0/188 0.0026 0.0131 1/138 0.0026 0.0131 1/533 0.0026 0.0131 1/533 0.0026 0.0033 0/78 0.0026 0.0047 0/192 0.0026 0.0041 1/15 0.0026 0.0041 1/157 0.0026 0.0040 0/933 0.0026 0.0040 0/344 0.0021 0.00069 0/134 0.002

Pooled rates of hematologic cancers in patients of IBD

Heterogeneity

Crohn's disease; *I*² = 27.14%, Q = 49.41, *P* = 0.068

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Ulcerative colitis; l^{2} = 31.66%, Q = 24.88, P = 0.098
Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); l^{2} = 71.29%, Q = 10.45, P = 0.015
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Overall; $l^2 = 34.25\%$, Q = 88.21, P = 0.0064

Figure 7. Meta-analysis of incidence rates of hematologic cancers among pediatric IBD. **A**, Forest plot of incidence rates of hematologic cancers among pediatric IBD. **B**, Funnel plot of the studies included in **Figure 7**, A. **The** Begg and Egger tests; P < .0001, <.0001, respectively. **C**, Funnel plot of the studies reporting the risk of hematologic cancers among patients with CD included in **Figure 7**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, <.0001, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **D**, Funnel plot of the studies reporting the risk of hematologic cancers among patients with UC included in **Figure 7**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, = .0033, respectively), but visual inspection of the funnel plot of the studies reporting of the risk of hematologic cancers among patients with UC included in **Figure 7**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, = .0033, respectively), but visual inspection of the funnel plot of the studies reporting of the risk of hematologic cancers among patients with IBD (studies that did not differentiate between CD and UC) included in **Figure 7**, A. There were no small-study effects or publication biases as assessed by the Begg and Egger tests (P = .73, .32, respectively).

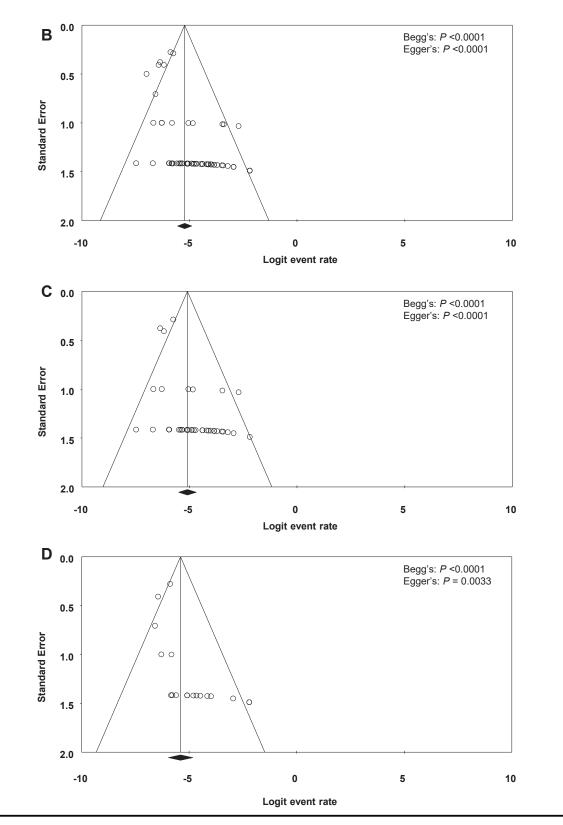


Figure 7. (Continued)

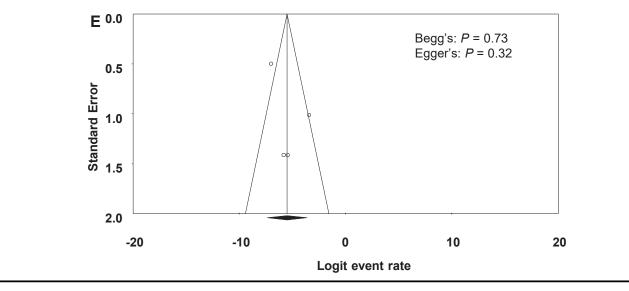


Figure 7. (Continued)

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	Event	Lower	Upper	Total	Event rate and 95% CI	Relative
Crohn's disease	rate	limit	limit	0 / 10	I	weight
Verhave et al. 1990 Gold et al. 1993 Gryboski et al. 1997 Markowitz et al. 1997 Markowitz et al. 2000 Stephens et al. 2003 de Ridder et al. 2004 Hyams et al. 2007 de Ridder et al. 2008 Duricova et al. 2009 Jakobsen et al. 2009 Jakobsen et al. 2009 Viola et al. 2009 Viola et al. 2009 Viola et al. 2009 Viola et al. 2010 Crombé et al. 2011 Kelsen et al. 2011 Kelsen et al. 2011 Kelsen et al. 2012 De Greef et al 2012 Hyams et al. 2012 Kierkus et al. 2012 Kierkus et al. 2012 Navas-López et al. 2013 Navas-López et al. 2014 Fumery et al. 2017 Mallet et al. 2017 Choi et al. 2018 Fang et al. 2018 Fang et al. 2018 Subtotal	$\begin{array}{c} 0.038\\ 0.031\\ 0.012\\ 0.021\\ 0.021\\ 0.0060\\ 0.0060\\ 0.0075\\ 0.0075\\ 0.0075\\ 0.0072\\ 0.0076\\ 0.0078\\ 0.0078\\ 0.0078\\ 0.0078\\ 0.0078\\ 0.0078\\ 0.0078\\ 0.0024\\ 0.0024\\ 0.00082\\ 0.0041\\ 0.0082\\ 0.0048\\ 0.0028\\ 0.0048\\ 0.0028\\ 0.0048\\ 0.0028\\ 0.0048\\ 0.0028\\ 0.0048\\ 0.0028\\ 0.0048\\ 0.0028\\ 0.0028\\ 0.0028\\ 0.0028\\ 0.0028\\ 0.0028\\ 0.0028\\ 0.0028\\ 0.0028\\ 0.0028\\ 0.0028\\ 0.015\\ 0.015\\ 0.015\\ 0.015\\ 0.0014\\ 0.0061\\ \end{array}$	0.0023 0.0019 0.00076 0.0013 0.00056 0.00038 0.00028 0.00028 0.00028 0.00028 0.00028 0.00028 0.00028 0.00037 0.00031 0.0013 0.0013 0.00051 0.00051 0.00051 0.00035 0.000417 0.000417 0.000417 0.000417 0.00041 0.00058 0.000410000000000	0.40 0.35 0.17 0.26 0.03 0.021 0.067 0.019 0.089 0.089 0.089 0.048 0.26 0.28 0.29 0.29 0.29 0.29 0.29 0.29 0.29 0.29	0 / 12 0 / 40 0 / 23 0 / 25 0 / 30 0 / 30 0 / 30 0 / 66 0 / 40 0 / 82 1 / 128 0 / 82 0 / 9 0 / 23 0 / 23 0 / 120 0 / 24 0 / 24 0 / 25 0 / 26 0 / 20 0 / 791 0 / 40 0 / 188 0 / 160 0 / 188 0 / 160 0 / 188 0 / 188 0 / 162 0 / 188 0 / 188 0 / 188 0 / 192 0 / 188 0 / 192 0 / 192 0 / 188 0 / 192 0 / 192 0 / 188 0 / 192 0 / 192 0 / 192 0 / 192 0 / 193 0 / 188 0 / 192 0 / 192 0 / 238 0 / 238 0 / 192 0 / 238 0 / 192 0 / 238 0 / 192 0 / 238 0 / 192 0 / 102 0 / 103 0 / 102 0 / 102 0 / 104 0 / 104 0 / 102 0 / 104 0 /		2.55597 2.22.2.660 2.22.2.2.660 2.22.2.660 2.22.2.660 2.22.2.660 2.22.2.660 2.22.2.660 2.22.2.660 2.22.2.2.2.2.2.2.2.2.2.2.2.2.2.2.2.2.2
Ulcerative colitis						
Ladd et al. 1935 Korelitz et al. 1965 Patterson et al. 1967 Verhave et al. 1990 Gold et al. 1990 Gold et al. 1993 Hyams et al. 1996 Långholz et al. 1997 Hyams et al. 2019 Hyams et al. 2019 Hyams et al. 2011 Ashworth et al. 2011 Peneau et al. 2011 Vahabnezhad et al. 2014 Hyams et al. 2017 Fang et al. 2018 Malham et al. 2019 Subtotal	$\begin{array}{c} 0.019\\ 0.0037\\ 0.0062\\ 0.011\\ 0.050\\ 0.10\\ 0.0029\\ 0.0062\\ 0.0082\\ 0.0084\\ 0.0094\\ 0.0094\\ 0.0004\\ 0.00035\\ 0.0035\\ 0.10\\ 0.00035\\ 0.10\\ 0.00080\\ 0.0074 \end{array}$	$\begin{array}{c} 0.0011\\ 0.00023\\ 0.00039\\ 0.00071\\ 0.0059\\ 0.00018\\ 0.00051\\ 0.00059\\ 0.00051\\ 0.00059\\ 0.00056\\ 0.00059\\ 0.00059\\ 0.00026\\ 0.00026\\ 0.00029$	0.24 0.056 0.091 0.16 0.67 0.091 0.13 0.091 0.13 0.013 0.013 0.013 0.021 0.0056 0.0056 0.0025 0.018	0 / 26 0 / 134 0 / 80 0 / 43 0 / 9 0 / 4 0 / 171 0 / 80 0 / 60 0 / 52 0 / 4 1 / 535 0 / 160 0 / 31 0 / 1,432 0 / 4 3 / 3,741 4 / 6,566		5555531 555554 555554 555554 555554 555554 555554 555555
Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis) Markowitz et al. 1993	0.0030 0.0044 0.016	0.00019 0.00028 0.00097	0.046 0.067 0.21	0 / 165 0 / 112 0 / 31 1 / 4,343 1 / 4, 365 1		23.25 23.24 23.11

Pooled rates of Hodgkin's lymphoma in patients of IBD

Heterogeneity

Crohn's disease; $l^2 = 23.20\%$, Q = 44.27, P = 0.34Ulcerative colitis; $l^2 = 50.99\%$, Q = 32.65, P = 0.18

Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); $l^2 = 57.56\%$, Q = 7.07, P = 0.070

Overall; *I*² = 36.77%, *Q* = 86.98, *P* = 0.075

Figure 8. Meta-analysis of incidence rates of Hodgkin lymphoma among pediatric IBD. **A**, Forest plot of incidence rates of Hodgkin lymphoma among pediatric IBD. **B**, Funnel plot of the studies included in **Figure 8**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, < .0001, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **C**, Funnel plot of the studies reporting the risk of Hodgkin lymphoma among patients with CD included in **Figure 8**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, = .0058, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **D**, Funnel plot of the studies reporting the risk of Hodgkin lymphoma among patients with UC included in **Figure 8**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, = .0058, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **D**, Funnel plot of the studies reporting the risk of Hodgkin lymphoma among patients with UC included in **Figure 8**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, = .0011, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **E**, Funnel plot of the studies reporting the risk of Hodgkin lymphoma among patients with IBD (studies that did not differentiate between CD and UC) included in **Figure 8**, A. There were no small-study effects or publication biases as assessed by the Begg test (P = .089), but were present by the Egger tests (P = .049). Visual inspection of the funnel plot appeared to show no asymmetry.

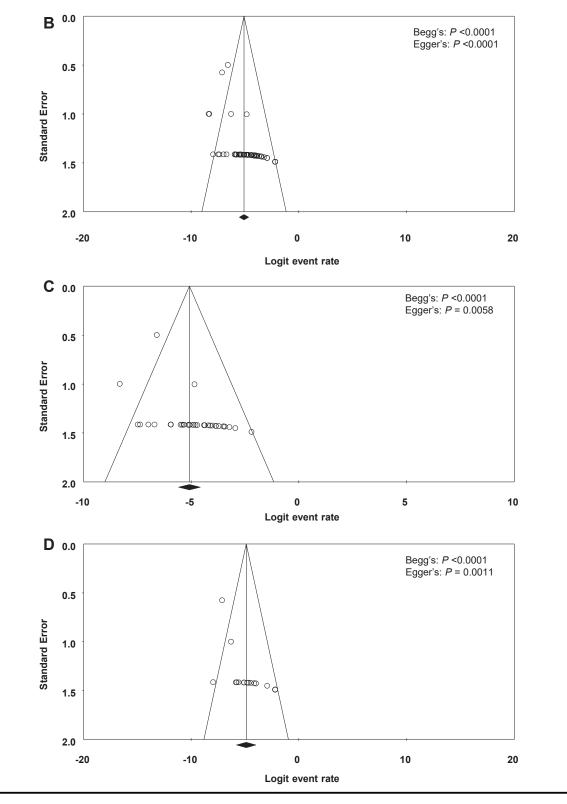


Figure 8. (continued)

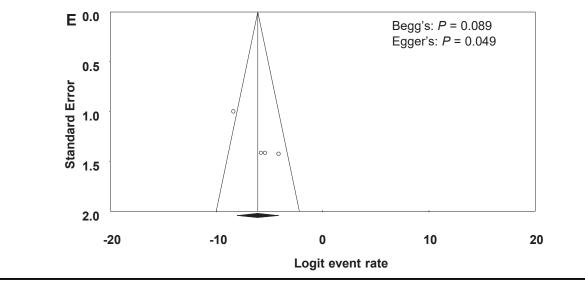


Figure 8. (continued)

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Study name	Event	Lower	Upper limit	Total	Event rate and 95% CI	Relativ weight
rohn's disease Verhave et al. 1990 Gold et al. 1993 Gryboski et al. 1993 Gryboski et al. 1994 Langholz et al. 2007 Markowitz et al. 2007 de Ridder et al. 2007 de Ridder et al. 2008 Vernier-Massouille et al. 2008 Urmis et al. 2009 Viola et al. 2009 Sinitsky et al. 2009 Sinitsky et al. 2009 Sinitsky et al. 2011 Hyams et al. 2011 Hyams et al. 2012 Hyams et al. 2012 Hyams et al. 2011 Ashworth et al. 2012 Hyams et al. 2012 Hyams et al. 2012 Hyams et al. 2012 Hyams et al. 2014 Hyams et al. 2014 Hyams et al. 2014 Hyams et al. 2015 Hyams et al. 2017 Choi et al. 2017 Choi et al. 2017 Choi et al. 2017 Hyams et al. 2017 Choi et al. 2018 Turner et al. 2019 ubtotal	rate 0.038 0.031 0.012 0.021 0.0089 0.0060 0.0060 0.0044 0.0075 0.0012 0.0050 0.050 0.050 0.050 0.021 0.021 0.024 0.0013 0.024 0.0013 0.0048 0.0026 0.0026 0.0049 0.0063 0.00083 0.00083 0.0026 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0005	limit 0.0024 0.0019 0.00076 0.0013 0.00056 0.00028 0.00028 0.00028 0.00028 0.00028 0.00024 0.00031 0.00031 0.00028 0.00026 0.00018 0.00026 0.00031 0.00047 0.00047 0.00058 0.00048 0.00047 0.00047 0.00058 0.00048 0.00040 0.00047 0.00047 0.00058 0.00040 0.00040 0.00047 0.00047 0.00058 0.00040 0.00040 0.00047 0.00058 0.00040 0.00058 0.00058 0.00050 0.00050 0.00038	0.40 0.40 0.357 0.17 0.26 0.067 0.011 0.059 0.067 0.17 0.26 0.34 0.063 0.12 0.063 0.063 0.063 0.063 0.0089 0.063 0.0089 0.0011 0.011 0.011 0.013 0.041 0.014 0.015 0.040 0.041 0.015 0.040 0.23 0.040 0.23 0.040 0.17 0.0020 0.0171	0 / 12 0 / 15 0 / 423 0 / 552 0 / 302 0 / 126 0 / 404 0 / 128 0 / 404 0 / 128 0 / 404 0 / 404 0 / 404 0 / 60 0 / 120 0 / 666 0 / 104 0 / 538 0 / 104 0 / 538 0 / 127 4 / 4,047 0 / 39 0 / 27 4 / 4,047 0 / 39 0 / 27 4 / 4,047 0 / 39 0 / 27 7 / 11,364		weigr 2.66 2.2777 2.27777 2.27777 2.27777 2.27777 2.277777777
Ilcerative colitis Ladd et al. 1935 Korelitz et al. 1965 Patterson et al. 1971 Verhave et al. 1990 Gold et al. 1993 Hyams et al. 1996 Lángholz et al. 1997 Jakobsen et al. 2009 Hyams et al. 2010 Kelsen et al. 2010 Kelsen et al. 2012 Peneau et al. 2012 Peneau et al. 2014 Hyams et al. 2017 Fang et al. 2017 Malham et al. 2019 Walham et al. 2019	$\begin{array}{c} 0.019\\ 0.0037\\ 0.0062\\ 0.010\\ 0.050\\ 0.010\\ 0.0029\\ 0.0062\\ 0.0082\\ 0.0082\\ 0.0094\\ 0.0093\\ 0.0031\\ 0.00050\\ 0.00050\\ 0.0072\\ \end{array}$	0.0011 0.00039 0.00071 0.0039 0.00071 0.0059 0.00018 0.00059 0.00059 0.00059 0.00059 0.00059 0.00058 0.00097 0.00097 0.00097 0.00093 0.00093 0.00093 0.00093 0.00093	0 24 0.056 0.091 0.48 0.67 0.045 0.091 0.12 0.67 0.015 0.048 0.21 0.0049 0.67 0.048 0.21 0.0049 0.67	0/26 0/134 0/80 0/43 0/9 0/4 0/171 0/80 0/60 0/52 0/4 0/535 0/4 0/535 0/31 1/1.432 0/4 2/3,741 3/6,566		$\begin{array}{c} 6.00\\ 6.11\\ 6.11\\ 5.94\\ 5.71\\ 6.11\\ 6.12\\ 6.12\\ 6.12\\ 6.12\\ 6.12\\ 5.74$ 5.74\\ 5.74\\ 5.74 5.74\\ 5.74 5.74 5.74 5.74 5.75
nflammatory bowel disease (no distinction etween Crohn's disease and ulcerative colitis) Markowitz et al. 1993 Lee et al. 2005 Choultaras et al. 2010 Colletit et al. 2013 ubtotal verall	0.0030 0.0044 0.032 0.00012 0.0036 0.0065	0.00019 0.0028 0.0045 0.000072 0.00077 0.0041	0.046 0.067 0.20 0.0018 0.017 0.010	0 / 165 0 / 112 1 / 31 0 / 4,343 1 / 4,551 11 / 22,581	0.00 0.50 1.0	22.08 22.06 33.74 22.12 0

Heterogeneity

Crohn's disease; *I*² = 32.70%, *Q* = 50.52, *P* = 0.034

Ulcerative colitis; *I*² = 52.12%, *Q* = 33.42, *P* = 0.0065

Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); $l^2 = 71.90\%$, Q = 10.67, P = 0.014

Overall; *I*² = 41.90%, *Q* = 94.66, *P* = 0.00071

Figure 9. Meta-analysis of incidence rates of non-Hodgkin lymphoma among pediatric IBD. **A**, Forest plot of incidence rates of non-Hodgkin lymphoma among pediatric IBD. **B**, Funnel plot of the studies included in **Figure 9**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, <.0001, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **C**, Funnel plot of the studies reporting the risk of non-Hodgkin lymphoma among patients with CD included in **Figure 9**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, =.00023, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **D**, Funnel plot of the studies reporting the risk of non-Hodgkin lymphoma among patients with UC included in **Figure 9**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, =.00013, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **D**, Funnel plot of the studies reporting the risk of non-Hodgkin lymphoma among patients with UC included in **Figure 9**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, =.00019, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **E**, Funnel plot of the studies reporting the risk of non-Hodgkin lymphoma among patients with IBD (studies that did not differentiate between CD and UC) included in **Figure 9**, A. There were no small-study effects or publication biases as assessed by the Begg and Egger tests (P = 1.00, .21, respectively).

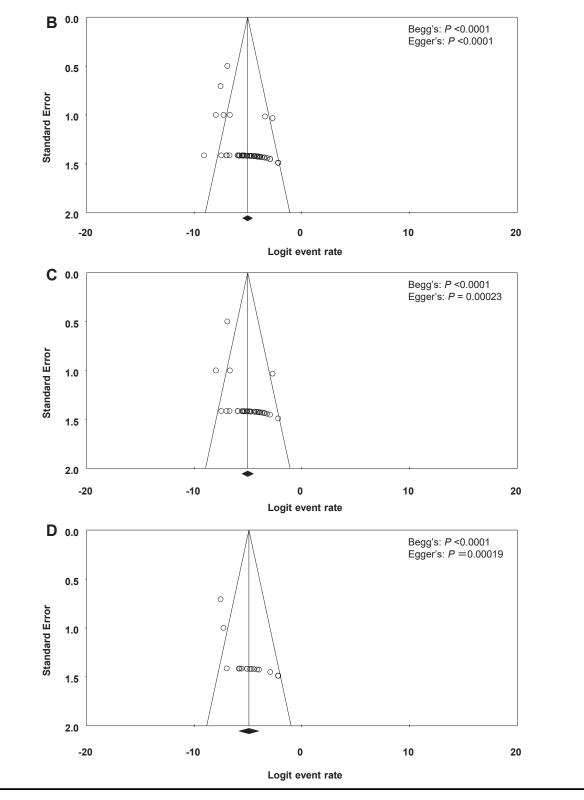


Figure 9. (continued)

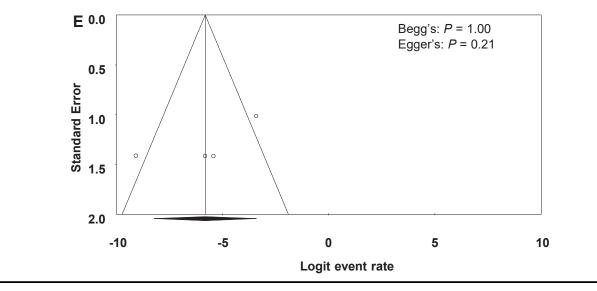


Figure 9. (Continued)

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Study name	Event	Lower	Upper	Total	Event	rate and 95	% CI	Relati
Crohn's disease Verhave et al. 1990 Gold et al. 1993 Gryboski et al. 1997 Markowitz et al. 2000 Stephens et al. 2003 de Ridder et al. 2004 Hyams et al. 2007 de Ridder et al. 2007 de Ridder et al. 2008 Duricova et al. 2009 Jakobsen et al. 2009 Jakobsen et al. 2009 Sinitsky et al. 2010 Crombé et al. 2010 Crombé et al. 2011 Hyams et al. 2011 Keisen et al. 2012 De Greef et al. 2012 De Greef et al. 2012 De Greef et al. 2012 Peneau et al. 2012 Nassa-López et al. 2013 Peneau et al. 2014 Rosh et al. 2014 Fush et al. 2014 Fush et al. 2014 Fush et al. 2015 Hyams et al. 2015 Hyams et al. 2017 Mallet et al. 2017 Mallet et al. 2017 Choi et al. 2018 Turrer et al. 2018 Subtotal	rate 0.038 0.031 0.012 0.021 0.0060 0.0060 0.0075 0.0012 0.0012 0.0021 0.0020 0.0020 0.021 0.021 0.021 0.029 0.0041 0.024 0.0024 0.0024 0.0024 0.0027 0.0026 0.0029 0.0027 0.0049 0.0029 0.0029 0.0029 0.0027 0.0049 0.0029 0.0029 0.0027 0.0049 0.0029 0.0029 0.0027 0.0029 0.0027 0.0029 0.0027 0.0029 0.0027 0.0029 0.0027 0.0029 0.0029 0.0029 0.0027 0.0029 0.0029 0.0027 0.0029 0.0029 0.0027 0.0029 0.0029 0.0029 0.0029 0.0029 0.0027 0.0029 0.0029 0.0029 0.0027 0.0029 0.0029 0.0029 0.0027 0.0029 0.0029 0.0027 0.0029 0.0027 0.0029 0.0029 0.0027 0.0029 0.0029 0.0027 0.0029 0.0029 0.0029 0.0029 0.0027 0.0029 0.0019 0.0026 0.0019 0.0026 0.0019 0.0015 0.00057 0.00057 0.00057 0.00057 0.0056 0.005	limit 0.0024 0.0019 0.00076 0.0013 0.00056 0.0013 0.00028 0.00047 0.00038 0.00024 0.0031 0.0013 0.0014 0.0013 0.0018 0.00051 0.00039 0.00039 0.00039 0.00039 0.00039 0.00039 0.00039 0.00039 0.00039 0.00039 0.00039 0.00039 0.00039 0.00047 0.00039 0.00039 0.00012 0.00012 0.00012 0.00032 0.00039 0.00012 0.00039 0.00012 0.00039 0.000039 0.000039 0.000039 0.00039 0.00039 0.00039 0.00039 0.	limit 0.40 0.35 0.17 0.26 0.13 0.089 0.21 0.067 0.19 0.089 0.059 0.059 0.063 0.22 0.29 0.20 0.20 0.011 0.013 0.093 0.023 0.023 0.041 0.013 0.020 0.020 0.0090 0.011	0 / 12 0 / 15 0 / 40 0 / 23 0 / 55 0 / 82 0 / 112 0 / 66 0 / 404 0 / 82 0 / 128 0 / 9 0 / 9 0 / 23 0 / 128 0 / 404 0 / 128 0 / 20 0 /		-		weig 222222222222222222222222222222222222
Ulcerative colitis Ladd et al. 1935 Koreiliz et al. 1962 Skyring et al. 1965 Patterson et al. 1971 Verhave et al. 1990 Gold et al. 1993 Hyams et al. 1996 Langhoiz et al. 1996 Hyams et al. 2009 Hyams et al. 2010 Kelsen et al. 2011 Kelsen et al. 2012 Peneau et al. 2012 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017 Subtotal	0 019 0.0037 0.0062 0.0510 0.050 0.0029 0.0062 0.0062 0.0083 0.0040 0.0040 0.0040 0.0040 0.0040 0.0040 0.0040 0.0040 0.0040 0.0040	0.0011 0.00023 0.00039 0.00071 0.0031 0.00059 0.00059 0.00059 0.00059 0.00059 0.00059 0.00059 0.00059 0.00059 0.000078 0.000978 0.000978	0.24 0.056 0.091 0.48 0.67 0.045 0.091 0.13 0.67 0.045 0.091 0.13 0.67 0.048 0.021 0.048 0.021 0.0049 0.021	0 / 26 0 / 134 0 / 80 0 / 43 0 / 9 0 / 4 0 / 141 0 / 80 0 / 62 0 / 535 0 / 545 0 0 / 545 0 0 / 545 0 0 / 141 1 / 1,432 1 / 2,821				62 662 662 662 662 662 662 662 662 662
Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis) Markowitz et al. 1993 Lee et al. 2003 Chouliaras et al. 2010 Colletit et al. 2013 Subtotal Overall	0.0030 0.0044 0.016 0.00023 0.0019 0.0056	0.00019 0.00028 0.00097 0.000032 0.00044 0.0028	0.046 0.067 0.21 0.0016 0.0078 0.011	0 / 165 0 / 112 0 / 31 1 / 4.343 1 / 4.651 5 / 15,876	- -			21.8 21.4 21.2 35.7
					0.00	0.50	1.00	
				Pool	ed rates of le	eukemia in p	atients o	of IBD
leterogeneity								
Crohn's disease; l^2 = 15.26%, Q = 37.76, P = 0.22								

Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); $l^2 = 57.56\%$, Q = 7.07, P = 0.070Overall; $l^2 = 24.20\%$, Q = 67.28, P = 0.063

Figure 10. Meta-analysis of incidence rates of leukemia among pediatric IBD. **A**, Forest plot of incidence rates of leukemia among patients with pediatric IBD. **B**, Funnel plot of the studies included in **Figure 10**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, < .0001, respectively), but visual inspection of the funnel plot appeared to show no asymmetry. **C**, Funnel plot of the studies reporting the risk of leukemia among patients with CD included in **Figure 10**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, < .0001, respectively). Visual inspection of the funnel plot appeared to show no asymmetry. **D**, Funnel plot of the funnel plot appeared to show no asymmetry. **D**, Funnel plot of the studies reporting the risk of leukemia among patients with UC included in **Figure 10**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, < .0001, < .0001, respectively). Visual inspection of the funnel plot appeared to show no asymmetry. **D**, Funnel plot of the studies reporting the risk of leukemia among patients with UC included in **Figure 10**, A. There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, = .0043, respectively). Visual inspection of the funnel plot appeared to show no asymmetry. **E**, Funnel plot of the studies reporting the risk of leukemia among patients with IBD (studies that did not differentiate between CD and UC) included in **Figure 10**, A. There were no small-study effects or publication biases as assessed by the Begg test (P = .089), but were present by the Egger tests (P = .049). Visual inspection of the funnel plot appeared to show no asymmetry.

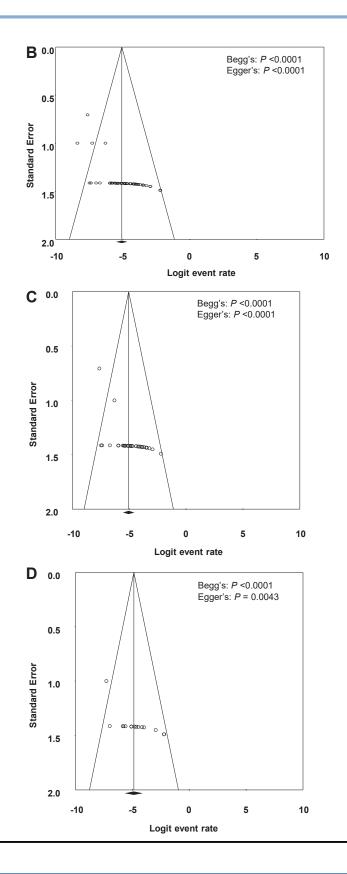


Figure 10. (continued)

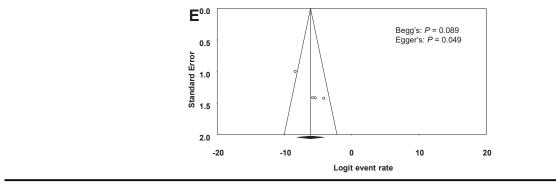


Figure 10. (Continued)

Α

Study name					_	Cumulative	rate ratio (95% CI)	
Crohn's disease	Point	Lower limit	Upper limit	Cohorts (n)					Rela wei
Jess et al. 2013	2.17	1.21	3.90	115					16.55
Peneau et al. 2013	2.25	1.36	3.73	653					22.34
Kappelman et al. 2014	2.28	1.66	3.13	NA			-		56.26
Malham et al. 2019	2.42	1.90	3.06	3,574+NA			-		100.00
Overall	2.42	1.90	3.06	3,574+NA			•		
Ulcerative colitis									
Jess et al. 2013	1.16	0.57	2.37	153					15.73
Peneau et al. 2013	2.04	0.54	7.69	313					21.04
Kappelman et al. 2014	1.87	1.11	3.17	NA					60.03
Malham et al. 2019	2.10	1.51	2.90	4,054+NA					100.00
Overall	2.10	1.51	2.90	4,054+NA			•		
Inflammatory bowel diseases (no distinction between Crohn's disease and ulcerative colitis)									
Coletti et al. 2013 (anti-TNF alpha exposed)	4.77	1.56	14.61	2,586					18.57
Coletti et al. 2013 (non biologic therapies)	4.90	2.08	11.53	4,343					31.82
Hyams et al. 2017	3.04	1.88	4.92	9,822			-	-	100.00
Overall	3.04	1.88	4.92	9,822					
					0.01	0.1	1	10	100
				Risk I	nigher amo	ng control	R	isk higher	among IBD

Figure 11. A, Cumulative meta-analysis of the overall risk of cancers reported as SIR among patients with pediatric IBD. B, Cumulative meta-analysis of incident rates of overall risk of cancers among patients with pediatric IBD. As the reporting years became more recent, the incidence of cancer was significantly reduced in the cumulative meta-analyses among CD, UC, and IBDs (regression coefficient 0.015, 0.039, 0.019, respectively. 95% CI 0.014-0.017 (P < .0001), 0.034-0.043 (P < .0001), 0.018-0.021 (P < .0001), respectively). **C**, Cumulative meta-analysis of the risk of CRC among patients with pediatric IBD. As the reporting years became more recent, the incidence of CRC was significantly reduced in the cumulative meta-analyses among CD. UC, and IBDs (regression coefficient 0.0018, 0.015, 0.0049, respectively. 95% CI 0.0016-0.0020 (P < .0001), 0.012-0.018 (P < .0001), 0.0043-0.0054 (P < .0001), respectively). **D**, Cumulative meta-analysis of the risk of hematologic cancers among patients with pediatric IBD. As the reporting years became more recent, the incidence of hematologic cancers was significantly reduced in the cumulative meta-analyses among CD, UC, and IBDs (regression coefficient 0.0020, 0.0021, 0.0018, respectively. 95% CI 0.0019-0.0021 (P < .0001), 0.0020-0.0022 (P < .0001), 0.0017-0.0019 (P < .0001), respectively). E, Cumulative analysis of the risk of Hodgkin lymphoma among patients with pediatric IBD. As the reporting years became more recent, the incidence of Hodgkin lymphoma was significantly reduced in the cumulative meta-analyses among CD, UC, and IBDs (regression coefficient 0.00033, 0.00060, 0.00034, respectively. 95% CI 0.00027-0.00040 (P < .0001), 0.00050-0.00069 (P < .0001), 0.00031-0.00038 (P < .0001), respectively). F, Cumulative meta-analysis of the risk of non-Hodgkin lymphoma among patients with pediatric IBD. As the reporting years became more recent, the incidence of non-Hodgkin lymphoma was significantly reduced in the cumulative meta-analyses among CD, UC, and IBDs (regression coefficient 0.00077, 0.00046, 0.00050, respectively. 95% CI 0.00072-0.00083 (P < .0001), 0.00040-0.00053 (P < .0001), 0.00047-0.00054 (P < .0001), respectively). G, Cumulative meta-analysis of the risk of leukemia among patients with pediatric IBD. As the reporting years became more recent, the incidence of leukemia was significantly reduced in the cumulative meta-analyses among CD, UC and IBDs (regression coefficient 0.00040, 0.00029, 0.00031, respectively. 95% CI 0.00035-0.00045 (P < .0001), 0.00016-0.00042 (P < .0001), 0.00028-0.00034 (P < .0001), respectively).

Study name				Cumulative rate ratio	
Crohn's disease	Lov Point lin	wer Upper nit limit	Event / total (n)		Relative weight
Weedon et al. 1973 Postuma et al. 1985 Verhave et al. 1990 Gold et al. 1993 Gryboski et al. 1994 Langholz et al. 1997 Markowitz et al. 2000 Stephens et al. 2003 de Ridder et al. 2003 de Ridder et al. 2004 Hyams et al. 2007 de Ridder et al. 2008 Duricova et al. 2009 Jakobsen et al. 2009 Jakobsen et al. 2009 Viola et al. 2009 Viola et al. 2009 Viola et al. 2009 Viola et al. 2010 Simitsky et al. 2010 Simitsky et al. 2011 Hyams et al. 2011 Crombé et al. 2011 Kelsen et al. 2011 Mavas-López et al. 2013 Nevas-López et al. 2013 Nevas-López et al. 2013 Nuti et al. 2014 Vahabnezhad et al. 2014 Fumer et al. 2017 Mallet et al. 2017 Mallet et al. 2017 Olen et al. 2017 Choi et al. 2018 Turner et al. 2018 Maham et al. 2019 Vorall	$\begin{array}{c} 0.027 & 0.0 \\ 0.027 & 0.0 \\ 0.028 & 0.0 \\ 0.027 & 0.0 \\ 0.027 & 0.0 \\ 0.027 & 0.0 \\ 0.025 & 0.0 \\ 0.025 & 0.0 \\ 0.025 & 0.0 \\ 0.024 & 0.0 \\ 0.024 & 0.0 \\ 0.024 & 0.0 \\ 0.024 & 0.0 \\ 0.024 & 0.0 \\ 0.020 & 0.0 \\ 0.017 & 0.0 \\ 0.017 & 0.0 \\ 0.015 & 0.0 \\ 0.015 & 0.0 \\ 0.015 & 0.0 \\ \end{array}$	115 0.037 114 0.036 113 0.032 113 0.030 113 0.030 113 0.030 113 0.030 113 0.030 113 0.030 114 0.030 114 0.030 114 0.030 114 0.029 114 0.028 113 0.026 113 0.026 113 0.026 113 0.027 110 0.027 110 0.024 110 0.024 110 0.023 110 0.024 110 0.024 110 0.024 110 0.024 111 0.024 111 0.024 111 0.024 111 0.024 111 0.024 1111 0.024 1111 </th <th>12 / 449 13 / 482 13 / 509 14 / 572 14 / 709 14 / 572 14 / 709 14 / 739 14 / 851 14 / 1,321 14 / 1,321 15 / 1,531 15 / 1,531 15 / 1,531 15 / 1,531 20 / 1,825 21 / 2,025 21 / 2,035 21 / 2,055 21 / 2,055 20 / 1 / 1,460 20 / 1 / 2,262 240 / 1 / 2,262</th> <th></th> <th>$\begin{array}{c} 523\\ 7.96\\ 9.75\\ 11.54\\ 14.28\\ 16.09\\ 17.92\\ 23.39\\ 25.22\\ 27.05\\ 28.88\\ 33.42\\ 33.52\\ 43.34\\ 35.24\\ 33.52\\ 41.73\\ 41.73\\ 41.53\\ 46.30\\ 48.12\\ 49.93\\ 55.42\\ 57.25\\ 57.25\\ 57.25\\ 57.42\\ 57.25\\ 57.25\\ 65.15\\ 69.99\\ 71.82\\ 76.42\\ 78.23\\ 83.47\\ 85.17\\ 90.83\\ 92.65\\ 94.48\\ 100.00\\ \end{array}$</th>	12 / 449 13 / 482 13 / 509 14 / 572 14 / 709 14 / 572 14 / 709 14 / 739 14 / 851 14 / 1,321 14 / 1,321 15 / 1,531 15 / 1,531 15 / 1,531 15 / 1,531 20 / 1,825 21 / 2,025 21 / 2,035 21 / 2,055 21 / 2,055 20 / 1 / 1,460 20 / 1 / 2,262 240 / 1 / 2,262		$\begin{array}{c} 523\\ 7.96\\ 9.75\\ 11.54\\ 14.28\\ 16.09\\ 17.92\\ 23.39\\ 25.22\\ 27.05\\ 28.88\\ 33.42\\ 33.52\\ 43.34\\ 35.24\\ 33.52\\ 41.73\\ 41.73\\ 41.53\\ 46.30\\ 48.12\\ 49.93\\ 55.42\\ 57.25\\ 57.25\\ 57.25\\ 57.42\\ 57.25\\ 57.25\\ 65.15\\ 69.99\\ 71.82\\ 76.42\\ 78.23\\ 83.47\\ 85.17\\ 90.83\\ 92.65\\ 94.48\\ 100.00\\ \end{array}$
Ulcerative colitis Ladd et al. 1935 Korelitz et al. 1962 Skyring et al. 1965 Devroede et al. 1971 Patterson et al. 1971 Michener et al. 1979 Verhave et al. 1990 Gold et al. 1993 Hyams et al. 1996 Langholz et al. 2099 Hyams et al. 2010 Kelsen et al. 2010 Kelsen et al. 2011 Jess et al. 2013 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017 Olen et al. 2019 Overall	0.056 0.0 0.075 0.0 0.070 0.0 0.056 0.0 0.058 0.0 0.048 0.0 0.044 0.0 0.031 0.0	335 0.11 333 0.094 338 0.13 338 0.13 328 0.13 328 0.11 129 0.11 129 0.11 125 0.092 123 0.079 122 0.074 123 0.075 126 0.074 123 0.075 126 0.066 124 0.066	1 / 26 10 / 160 13 / 240 65 / 636 67 / 679 77 / 1,012 77 / 1,025 79 / 1,196 80 / 1,276 82 / 1,336 82 / 1,336 82 / 1,336 82 / 1,338 82 / 1,332 91 / 1,545 94 / 1,736 94 / 1,736 95 / 1,1557 435 / 11,557		3.87 11.11 17.08 25.05 30.28 37.64 40.15 42.58 47.88 51.81 57.07 62.09 69.34 75.33 77.91 83.93 92.06 100.00
Inflammatory bowel diseases (no distibutive between Crohn's disease and ulcerativ Markowitz et al. 1993 Lee et al. 2005 Chouliaras et al. 2010 Colletti et al. 2013 El-Matary et al. 2020 Overall		0510.0250210.0460970.0220150.030	0 / 165 0 / 277 1 / 308 8 / 4,651 25 / 5,598 25 / 5,598		14.28 28.56 47.21 73.12 100.00

Univariate regression analyses for the slope of cumulative analyses

Crohn's disease; regression coefficient 0.015, 95% CI 0.014-0.017 (*P* <0.0001) Ulcerative colitis; regression coefficient 0.039, 95% CI 0.034-0.043 (*P* <0.0001) Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); regression coefficient 0.0036, 95% CI 0.00019-0.0069 (*P* = 0.044)

Overall; regression coefficient 0.019, 95% CI 0.018-0.021 (*P* <0.0001)

Figure 11. (continued)

С

Study name		Lawar	Unner	Event /	Cumulative rate ratio (95% CI)	Deletive
Crohn's disease	Point	Lower limit	Upper limit	Event / total (n)		Relative weight
Weedon et al. 1973 Postuma et al. 1985 Verhave et al. 1990 Gold et al. 1993 Gillen et al. 1994 Gryboski et al. 1994 Langholz et al. 1997 Markowitz et al. 2007 de Ridder et al. 2003 de Ridder et al. 2007 de Ridder et al. 2007 de Ridder et al. 2007 de Ridder et al. 2009 Hyams et al. 2009 Jakobsen et al. 2009 Viola et al. 2010 Simitsky et al. 2010 Simitsky et al. 2011 Kelsen et al. 2011 Kelsen et al. 2011 Kelsen et al. 2012 Assa et al. 2013 Avasa-López et al. 2013 Avasa-López et al. 2013 Peneau et al. 2014 Vahabnezhad et al. 2014 Fummy et al. 2017 Mallet et al. 2017 Mallet et al. 2017 Choi et al. 2018 Malham et al. 2019 Olén et al. 2018 Malham et al. 2020 Derall	0.018 0.018 0.023 0.022 0.022 0.022 0.022 0.021 0.020 0.019 0.018 0.017 0.017 0.017 0.017 0.017 0.017 0.017 0.017 0.017 0.016 0.016 0.016 0.016 0.016 0.016 0.015 0.017 0.017 0.017 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.017 0.017 0.015 0.015 0.015 0.015 0.017 0.017 0.015 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.0055 0.0075	0 0089 0 00900 0 0096 0 0010 0 013 0 013 0 013 0 013 0 013 0 013 0 013 0 013 0 011 0 001 0 000 0 0000 0 000 0 0000 0 0000 0 0000 0 0000 0 0000 0 0000 0 0000 0 00000 0 0000 0 0000 0 0000 0 0000 0 00000 0 00000 0 0000 0 00000 0 00000 0 00000 0 00000 0 000000	0 035 0 034 0 035 0 038 0 037 0 037 0 037 0 037 0 037 0 037 0 034 0 033 0 031 0 034 0 026 0 026 0 026 0 026 0 026 0 026 0 022 0 002 0 022 0 002 0 001 0 001	$\begin{array}{c} 8 / 449 \\ 8 / 494 \\ 8 / 609 \\ 12 / 662 \\ 12 / 665 \\ 12 / 685 \\ 12 / 740 \\ 12 / 822 \\ 12 / 852 \\ 12 / 740 \\ 12 / 1030 \\ 12 / 1.344 \\ 12 / 1.516 \\ 12 / 1.516 \\ 12 / 1.633 \\ 12 / 1.716 \\ 15 / 2.118 \\ 15 / 2.118 \\ 15 / 2.242 \\ 15 / 2.988 \\ 15 / 2.2118 \\ 15 / 2.242 \\ 15 / 2.988 \\ 15 / 2.2118 \\ 15 / 2.242 \\ 15 / 2.2430 \\ 15 / 2.244 \\ 15 / 2.244 \\ 15 / 2.244 \\ 15 / 2.2614 \\ 15 / 2.2614 \\ 15 / 2.2614 \\ 15 / 2.2614 \\ 15 / 2.2614 \\ 16 / 3.579 \\ 16 / 7.653 \\ $		$\begin{array}{c} 6.88\\ 8.69\\ 10.47\\ 12.26\\ 18.03\\ 19.84\\ 21.65\\ 23.47\\ 25.29\\ 27.11\\ 28.93\\ 30.76\\ 32.29\\ 27.11\\ 28.93\\ 30.76\\ 32.59\\ 34.42\\ 36.01\\ 38.01\\ 39.82\\ 41.43\\ 46.65\\ 52.33\\ 54.95\\ 57.78\\ 59.61\\ 44.88\\ 48.67\\ 55.33\\ 55.61\\ 61.44\\ 68.24\\ 66.24\\ 66.24\\ 66.24\\ 66.24\\ 66.24\\ 66.24\\ 66.24\\ 66.24\\ 66.24\\ 66.24\\ 66.24\\ 66.24\\ 66.24\\ 66.24\\ 66.24\\ 68.55\\ 84.18\\ 94.18\\ 100.00\\ \end{array}$
Ilcerative colitis						
Ladd et al. 1935 Lagercrantz et al. 1955 Michener et al. 1961 Hijmans et al. 1962 Korelitz et al. 1962 Skyring et al. 1962 Skyring et al. 1962 Binder et al. 1971 Binder et al. 1973 Michener et al. 1973 Werhave et al. 1990 Ahsgren et al. 1993 Gold et al. 1993 Gold et al. 1996 Langholz et al. 1996 Langholz et al. 1997 Falcone et al. 2000 Gower-Rousseau et al. 2009 Jakobsen et al. 2000 Kelsen et al. 2010 Kelsen et al. 2011 Vahabnezhad et al. 2014 Hyams et al. 2017 Olén et al. 2019 Dien et al. 2019 Dien et al. 2019 Dien et al. 2019	0.038 0.043 0.053 0.078 0.069 0.060 0.047 0.042 0.047 0.042 0.041 0.042 0.038 0.036 0.036 0.034 0.031 0.032 0.031 0.032 0.029 0.029 0.029 0.025 0.021 0.020	0.0050 0.021 0.028 0.041 0.034 0.028 0.027 0.025 0.023 0.023 0.023 0.023 0.023 0.023 0.023 0.023 0.024 0.020 0.019 0.018 0.019 0.018 0.019 0.017 0.014 0.015 0.012 0.012	$\begin{array}{c} 0.23\\ 0.087\\ 0.098\\ 0.14\\ 0.13\\ 0.11\\ 0.099\\ 0.092\\ 0.085\\ 0.076\\ 0.072\\ 0.073\\ 0.066\\ 0.072\\ 0.073\\ 0.066\\ 0.062\\ 0.053\\ 0.053\\ 0.054\\ 0.053\\ 0.054\\ 0.053\\ 0.054\\ 0.053\\ 0.054\\ 0.043\\ 0.043\\ 0.034\\ 0.034\\ \end{array}$	1 / 26 7 / 163 9 / 181 55 / 582 55 / 625 60 / 759 62 / 839 63 / 882 63 / 926 72 / 1,259 72 / 1,268 72 / 1,300 72 / 1,304 74 / 1,475 75 / 1,555 75 / 1,628 76 / 1,741 78 / 1,853 78 / 1,853 78 / 1,853 79 / 2,017 79 / 2,048 79 / 3,480 175 / 8,128 187 / 11,869 203 / 13,787 203 / 13,787		3.45 8.97 13.32 19.48 21.90 27.30 31.77 35.24 43.42 45.78 48.20 50.48 54.97 58.46 60.89 64.38 64.38 68.84 71.55 77.05 79.46 81.90 88.13 94.02 100.00
Inflammatory bowel diseases (no dis between Crohn's disease and ulcera Markowitz et al. 1993		0.00019	0.046	0 / 165	►	25.03
Lee et al. 2005 Chouliaras et al. 2010 Colletti et al. 2013 Overall	0.0037 0.0059 0.0022 0.0022	0.00051 0.0012 0.00028 0.00028	0.025 0.029 0.017 0.017	0 / 277 0 / 308 0 / 4,651 0 / 4,651		50.05 74.93 100.00

Crohn's disease; regression coefficient 0.0018, 95% Cl 0.0016-0.0020 (P <0.0001) Ulcerative colitis; regression coefficient 0.015, 95% Cl 0.012-0.018 (P <0.0001)

Distance Galls, regression Coefficient 0.012, 93/8 CI 0.012-0.016 (r < 0.0001) Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); regression coefficient NA, 95% CI NA Overall; regression coefficient 0.0049, 95% CI 0.0043-0.0054 (P <0.0001)</p>

Figure 11. (continued)

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Study name			11	Ev. 11	Cumulative rate ratio (95% CI)	
Crohn's disease	Point	Lower limit	Upper limit	Event / total (n)		Relativ weigh
Postuma et al. 1985 Verhave et al. 1990 Gold et al. 1993 Gryboski et al. 1994 Langholz et al. 1997 Markowitz et al. 2000 Stephens et al. 2000 de Ridder et al. 2003 de Ridder et al. 2007 de Ridder et al. 2007 de Ridder et al. 2009 Uricova et al. 2009 Hyams et al. 2009 Jakobsen et al. 2009 Wiola et al. 2009 Sinitsky et al. 2009 Sinitsky et al. 2010 Crombé et al. 2011 Hyams et al. 2011 Keisen et al. 2011 Ashworth et al. 2011 De Greef et al 2012 Hyams et al. 2012 De Greef et al. 2012 Assa et al. 2013 Peneau et al. 2013 Nuti et al. 2014 Kierkus et al. 2014 Kababa et al. 2014 Mahabnezhad et al. 2014 Fumery et al. 2015 Hyams et al. 2017 Olen et al. 2017 Choi et al. 2018 Turner et al. 2019 Overall	0.030 0.033 0.032 0.027 0.026 0.019 0.018 0.016 0.015 0.011 0.011 0.011 0.012 0.0094 0.0094 0.0088 0.0088 0.0069 0.0067 0.0069 0.0067 0.0069 0.0067 0.0069 0.0067 0.0069 0.0067 0.0069 0.0067 0.0069 0.0067 0.0069 0.0067 0.0069 0.0067 0.0069 0.0067 0.0069 0.0067 0.0069 0.0067 0.0069 0.0067 0.0069 0.0067 0.0069 0.0067 0.0069 0.0067 0.0069 0.0067 0.0067 0.0069 0.00669 0.00661 0.0061 0.0061 0.0061 0.0061 0.0061 0.0065 0.00661 0.00	$\begin{array}{c} 0.0043\\ 0.0066\\ 0.0081\\ 0.0077\\ 0.0083\\ 0.0077\\ 0.0073\\ 0.0070\\ 0.0070\\ 0.0070\\ 0.0070\\ 0.0073\\ 0.0064\\ 0.0053\\ 0.0064\\ 0.0053\\ 0.0064\\ 0.0065\\ 0.0064\\ 0.0068\\ 0.0065\\ 0.0068\\ 0.0065\\ 0.0068\\ 0.0055\\ 0.0056\\ 0.0055\\ 0.005\\ 0$	0.19 0.15 0.15 0.088 0.076 0.049 0.049 0.024 0.024 0.022 0.024 0.023 0.024 0.023 0.024 0.023 0.024 0.022 0.022 0.022 0.022 0.024 0.023 0.024 0.023 0.024 0.023 0.024 0.023 0.024 0.025 0.016 0.016 0.016 0.016 0.015 0.015 0.014 0.014 0.014 0.014 0.014 0.014 0.014 0.014 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.014 0.014 0.014 0.014 0.014 0.014 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.015 0.014 0.014 0.014 0.015 0.014 0.014 0.014 0.015 0.015 0.014 0.014 0.015 0.014 0.014 0.015 0.015 0.014 0.014 0.015 0.015 0.014 0.015 0.005	1 / 33 1 / 45 1 / 60 1 / 100 1 / 123 1 / 178 1 / 290 1 / 402 1 / 468 1 / 872 2 / 1,091 2 / 1,191 2 / 1,191 3 / 2,265 3 / 2,265 3 / 2,265 3 / 2,265 3 / 2,265 5 / 3,245 6 / 3,629 13 / 7,667 6 / 3,629 13 / 7,680 25 / 11,481 25 / 11,481 25 / 11,481 25 / 11,283 31 / 15,283		$\begin{array}{c} 3.22\\ 5.00\\ 8.77\\ 10.66\\ 12.55\\ 14.33\\ 16.22\\ 14.33\\ 16.22\\ 21.97\\ 27.72\\ 27.72\\ 27.72\\ 27.72\\ 27.72\\ 28.84\\ 30.27\\ 28.84\\ 30.27\\ 32.42\\ 33.42\\ 47.12\\ 47.12\\ 47.12\\ 49.02\\ 54.90\\ 54.90\\ 54.90\\ 55.73\\ 59.22\\ 55.92$
Ulcerative colitis Ladd et al. 1935 Korelitz et al. 1962 Skyring et al. 1965 Patterson et al. 1971 Michener et al. 1979 Verhave et al. 1990 Gold et al. 1993 Hyams et al. 1996 Langholz et al. 1997 Jakobsen et al. 2009 Hyams et al. 2010	0.019 0.0083 0.0075 0.0083 0.0059 0.0080 0.011 0.0093 0.0089 0.0089	0.0011 0.0012 0.0015 0.0019 0.0028 0.0040 0.0037 0.0037 0.0038 0.0040	0.24 0.056 0.033 0.018 0.023 0.023 0.023 0.021 0.020	0 / 26 0 / 160 0 / 240 0 / 283 1 / 616 1 / 625 1 / 629 1 / 800 1 / 880 1 / 940 1 / 992		3.41 6.87 10.32 13.75 19.76 23.08 26.25 29.71 33.16 36.60 40.04
Kelsen et al. 2011 Ashworth et al. 2012 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017 Olen et al. 2017 Malham et al. 2019 Overall	0.0003 0.011 0.0084 0.0079 0.0082 0.0065 0.0054 0.0054 0.0045 0.0045	0.0049 0.0041 0.0039 0.0042 0.0033 0.0030 0.0026 0.0026	0.023 0.017 0.016 0.016 0.013 0.0098 0.0079 0.0079	1 / 996 2 / 1,531 2 / 1,691 2 / 1,722 4 / 3,154 17 / 7,802 23 / 11,543 23 / 11,543		43.21 49.23 52.68 56.11 65.63 84.42 100.00
Inflammatory bowel diseases (no between Crohn's disease and ulo)				
Markowitz et al. 1993 Lee et al. 2005 Chouliaras et al. 2010 Colletti et al. 2013 Overall	0.0030 0.0037 0.010 0.0041 0.0041	0.00019 0.00051 0.0021 0.0063 0.0063	0.046 0.025 0.046 0.026 0.026	0 / 165 0 / 277 1 / 308 5 / 4,651 5 / 4,651		20.29 40.5 66.5 100.00

Univariate regression analyses for the slope of cumulative analyses

Crohn's disease; regression coefficient 0.0020, 95% CI 0.0019-0.0021 (P < 0.0001) Ulcerative colitis; regression coefficient 0.0021, 95% CI 0.0020-0.0022 (P < 0.0001) Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); regression coefficient 0.0011, 95% CI 0.00047-0.0017 (P = 0.016) Overall; regression coefficient 0.0018, 95% CI 0.0017-0.0019 (P < 0.0001)

Figure 11. (continued)

Ε

Study name		Lower	Upper	Event /	Cumulative rate ratio (95% C	I) Relative
Crohn's disease	Point	limit	limit	total (n)		weight
Verhave et al. 1990 Gold et al. 1993	0.039 0.035	0.0024 0.0049	0.40 0.21	0 / 12 0 / 27 0 / 67		2.53 5.08
Gryboski et al. 1994	0.024 0.024	0.0049	0.11	0/67	■	7.67
Langholz et al. 1997 Markowitz et al. 2000	0.024	0.0059 0.0056	0.089 0.065	0 / 90 0 / 145	-	10.24 12.84
Stephens et al. 2003	0.016	0.0051	0.048	0 / 227	•	15.44
de Ridder et al. 2004	0.016	0.0056	0.045	0 / 257		18.02
Hyams et al. 2007 de Ridder et al. 2008	0.014 0.013	0.0051 0.0050	0.036 0.032	0 / 369 0 / 435	- I I	20.63 23.22
Vernier-Massouille et al. 2008	0.010	0.0042	0.024	0 / 839		23.22 25.84
Duricova et al. 2009 Hyams et al. 2009	0.0096 0.0093	0.0041 0.0043	0.022 0.020	0 / 921 1 / 1,049		28.44 32.77
Jákobsen et al. 2009	0.010	0.0050	0.022	1 / 1,058	-	35.28 37.87
Ruemmele et al. 2009	0.011	0.0052	0.021	1 / 1,098		37.87
Viola et al. 2009 Sinitsky et al. 2010	0.011 0.012	0.0055 0.0059	0.022 0.023	1 / 1,121 1 / 1,137	• I I	40.44 42.99
Crombé et al. 2011	0.011	0.0057	0.021	1 / 1.257		45.60
Hyams et al. 2011 Kelsen et al. 2011	0.011 0.011	0.0057 0.0061	0.020 0.021	1 / 1,317 1 / 1,337	F	48.20 50.76
Ashworth et al. 2012	0.0098	0.0054	0.018	1 / 2,128 1 / 2,232 1 / 2,420 1 / 2,486		53.37
De Greef et al 2012	0.0095 0.0090	0.0053 0.0050	0.017 0.016	1/2,232		55.98 58.59
Hyams et al. 2012 Kierkus et al. 2012	0.0089	0.0051	0.016	1 / 2,420	•	61.19
Assa et al. 2013	0.0087	0.0050	0.015 0.016	1/2,588		63.79 66.34
Assa et al. 2013 Navas-López et al. 2013 Peneau et al. 2013	0.0091 0.0084	0.0053 0.0049	0.016	1 / 2,588 1 / 2,604 1 / 3,142 1 / 3,220	•	66.34 68.96
Nuti et al. 2014	0.0083	0.0049	0.014	1/3,220		71.56
Rosh et al. 2014 Fumery et al. 2015	0.0079 0.0082	0.0047 0.0049	0.013 0.014	1/3,412		74.17 76.74
Hvams et al. 2017	0.0066	0.0040	0.011	2 / 7,486		81.10
Mallet et al. 2017 Choi et al. 2018	0.0072 0.0073	0.0043 0.0045	0.012 0.012	2 / 7,490		83.50 86.09
Fang et al. 2018	0.0073	0.0046	0.012	2 / 7,486 2 / 7,490 2 / 7,523 2 / 7,562	•	88.67
Fang et al. 2018 Turner et al. 2018 Malham et al. 2010	0.0069	0.0043	0.011	2 / 8,443 6 / 11,364		91.29
Malham et al. 2019 Overall	0.0061 0.0061	0.0037 0.0037	0.010 0.010	6 / 11,364	•	100.00
Ladd et al. 1935 Korelitz et al. 1962 Skyring et al. 1965 Patterson et al. 1971 Verhave et al. 1990 Gold et al. 1993 Hyams et al. 1996 Langholz et al. 1997 Jakobsen et al. 2010 Kelsen et al. 2011 Ashworth et al. 2012 Peneau et al. 2013	0.019 0.0083 0.0075 0.0083 0.012 0.017 0.013 0.012 0.011 0.011 0.011 0.013 0.0099 0.0091	0.0011 0.0012 0.0021 0.0034 0.0053 0.0045 0.0045 0.0046 0.0058 0.0045 0.0045	0.236 0.056 0.033 0.040 0.051 0.036 0.031 0.028 0.026 0.031 0.021 0.021	0 / 26 0 / 160 0 / 240 0 / 283 0 / 292 0 / 296 0 / 467 0 / 547 0 / 607 0 / 659 0 / 663 1 / 1,198 1 / 1,358		5.51 11.06 16.61 22.14 27.55 32.79 38.35 43.90 49.44 54.97 60.22 67.88 73.44
Vahabnezhad et al. 2014	0.0094	0.0046	0.019	1 / 1,389	•	78.95
Hyams et al. 2017	0.0079	0.0037	0.017	1 / 2,821		84.52
Fang et al. 2018	0.0092	0.0042	0.020	1 / 2,825		89.76
Malham et al. 2019 Dverall	0.0074 0.0074	0.0031 0.0031	0.018 0.018	4 / 6,566 4 / 6,566	.	100.00
Inflammatory bowel diseases (no dist Crohn's disease and ulcerative colitis		n				
Markowitz et al. 1993	0.0030	0.00019	0.046	0 / 165		23.25
Lee et al. 2005	0.0037	0.00051	0.025	0 / 277		46.49
Chouliaras et al. 2010	0.0059	0.0012	0.029	0/308		69.60
Colletti et al. 2013 Overall	0.0022 0.0022	0.00031 0.00031	0.015 0.015	1 / 4,651 1 / 4,651	•	100.00
	0.0022	0.00001	0.010	1, 4,001		

Chorn's disease, regression coefficient 0.0003, 95% CI 0.0027-0.00040 (P < 0.0001) Ulcerative colitis; regression coefficient 0.00060, 95% CI 0.00050-0.00069 (P < 0.0001) Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); regression coefficient 0.00023, 95% CI 0.00021-0.00025 (P = 0.00039) Overall; regression coefficient 0.00034, 95% CI 0.00031-0.00038 (P < 0.0001)

Figure 11. (continued)

Study name					Cumulative rate ratio (95% CI)	
rohn's disease	Point	Lower limit	Upper limit	Event / total (n)		Relative weight
Verhave et al. 1990 Gold et al. 1993 Gryboski et al. 1994 Langholz et al. 1997 Markowitz et al. 2000 Stephens et al. 2003 de Ridder et al. 2004 Hyams et al. 2007 de Ridder et al. 2008 Uvrnier-Massouille et al. 2008 Duricova et al. 2009 Jakobsen et al. 2009 Jakobsen et al. 2009 Viola et al. 2009 Sinitsky et al. 2010 Crombé et al. 2011 Hyams et al. 2011 Kelsen et al. 2011 De Greef et al. 2011 De Greef et al. 2012 Hyams et al. 2012 Hyams et al. 2012 Hyams et al. 2013 Navas-López et al. 2013 Nuti et al. 2014 Fumery et al. 2014 Fumery et al. 2015 Hyams et al. 2017 Mallet et al. 2017 Mallet et al. 2018 Fang et al. 2018 Turner et al. 2018 Malham et al. 2019 verall	0.039 0.025 0.024 0.079 0.016 0.016 0.016 0.013 0.013 0.010 0.0086 0.0089 0.0080 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.011 0.0087 0.0083 0.0082 0.0084 0.0085 0.0085 0.0074 0.0075 0.0071 0.0065 0.0065	0.0024 0.0049 0.0059 0.0059 0.0051 0.0051 0.0051 0.0051 0.0042 0.0042 0.0042 0.0042 0.0042 0.0045 0.0055 0.0055 0.0055 0.0055 0.0055 0.0055 0.0049 0.0048 0.0048 0.0046 0.0047 0.0046 0.0047 0.0048 0.0047 0.0048 0.0047 0.0048 0.0051 0.0051 0.0055 0.0042 0.0042 0.0042 0.0042 0.0045 0.0043 0.0044 0.0043 0.0043 0.0043 0.0043 0.0043 0.0043 0.0043 0.0043 0.0043 0.0043 0.0043 0.0043 0.0043 0.0043 0.0038 0.0038 0.0038	0.40 0.21 0.11 0.089 0.065 0.045 0.032 0.021 0.021 0.021 0.016 0.014 0.014 0.014 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.014 0.011 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.012 0.011 0.014 0.011 0.012 0.012 0.012 0.012 0.012 0.011 0.011 0.011 0.012 0.012 0.012 0.011 0.011 0.011 0.011 0.011 0.011 0.012 0.012 0.012 0.011 0.011 0.011 0.011 0.012 0.012 0.012 0.011 0.011 0.012 0.012 0.012 0.012 0.012 0.012	0 / 12 0 / 27 0 / 67 0 / 90 0 / 227 0 / 369 0 / 435 0 / 839 0 / 1068 0 / 1068 0 / 1068 0 / 1098 0 / 1098 0 / 1098 0 / 1,121 0 / 1,127 0 / 1,237 0 / 1,217 0 / 1,217 0 / 1,217 0 / 1,237 1 / 2,232 1 / 2,486 1 / 2,232 1 / 2,486 1 / 2,2604 2 / 3,142 2 / 3,442 2 / 3,443 7 / 11,364 7 / 11,364		$\begin{array}{c} 2.56\\ 5.14\\ 7.75\\ 10.34\\ 12.96\\ 15.58\\ 18.19\\ 20.81\\ 23.43\\ 26.06\\ 39.06\\ 41.64\\ 44.26\\ 46.88\\ 49.47\\ 53.58\\ 56.20\\ 56.20\\ 58.83\\ 61.45\\ 64.08\\ 68.04\\ 70.67\\ 773.92\\ 78.52\\ 85.60\\ 88.04\\ 90.65\\ 93.26\\ 93.26\\ 95.89\\ 100.00\\ \end{array}$
licerative colitis						
Ladd et al. 1935 Korelitz et al. 1962 Skyring et al. 1965 Patterson et al. 1971 Verhave et al. 1990 Gold et al. 1993 Hyams et al. 1996 Langholz et al. 1997 Jakobsen et al. 2009 Hyams et al. 2010 Kelsen et al. 2011 Ashworth et al. 2011 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017 Fang et al. 2018 Malham et al. 2019 Verall	0.019 0.0083 0.0075 0.0083 0.012 0.017 0.013 0.012 0.011 0.013 0.011 0.013 0.011 0.013 0.011 0.0097 0.010 0.0097 0.00072 0.0072 0.0072	0.0011 0.0012 0.0015 0.0021 0.0034 0.0045 0.0045 0.0044 0.0045 0.0046 0.0048 0.0048 0.0045 0.0048 0.0045 0.0048 0.0045 0.0048 0.0049 0.0029 0.0029	0.24 0.056 0.036 0.033 0.040 0.051 0.036 0.031 0.028 0.028 0.026 0.031 0.024 0.021 0.021 0.021 0.017 0.020 0.018 0.018	0 / 26 0 / 160 0 / 240 0 / 283 0 / 292 0 / 296 0 / 467 0 / 547 0 / 659 0 / 663 0 / 1,188 0 / 1,358 0 / 1,389 1 / 2,821 1 / 2,825 3 / 6,566 3 / 6,566		5.58 11.20 16.81 22.41 27.89 33.22 38.84 44.45 50.06 55.67 60.99 66.62 72.24 77.83 85.44 90.76 100.00
nflammatory bowel diseases (no di etween Crohn's disease and ulcera Markowitz et al. 1993 Lee et al. 2005		0.00019 0.00051	0.046 0.025	0 / 165 0 / 277		23.91 47.81

Univariate regression analysis for the slope of cumulative analysis

Crohn's disease; regression coefficient 0.00077, 95% CI 0.00072-0.00083 (P <0.0001) Ulcerative colitis; regression coefficient 0.00046, 95% CI 0.00042-0.00053 (P <0.0001) Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); regression coefficient 0.00016, 95% CI -0.00049-0.00080 (P = 0.41) Overall; regression coefficient 0.00050, 95% CI 0.00047-0.00054 (P <0.0001)

Figure 11. (continued)

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Lower Upper Event / Verhave et al. 1990 0.039 0.0024 0.40 0.11 Verhave et al. 1990 0.039 0.0044 0.41 0.127 Corbertal. 1 al. 1994 0.024 0.0049 0.11 0.77 Langholz et al. 1997 0.024 0.0059 0.081 0.767 Markowitz et al. 2000 0.020 0.0056 0.046 0.7227 de Ridder et al. 2003 0.016 0.0051 0.0448 0.7227 de Ridder et al. 2004 0.016 0.0051 0.048 0.7227 de Ridder et al. 2009 0.011 0.0051 0.022 0.73845 Duricova et al. 2009 0.010 0.0042 0.022 0.71.058 Ruemmete et al. 2019 0.011 0.0055 0.021 0.71.317 viale et al. 2011 0.011 0.0055 0.021 0.71.317 keisen et al. 2011 0.011 0.0055 0.021 0.71.317 keisen et al. 2011 0.011 0.0055 0.022 0.71.317	nulative rate ratio (95% CI	l) Relative
Gold et al. 1993 0.035 0.0049 0.21 0 / 27 Gryboski et al. 1997 0.024 0.0095 0.089 0 / 90 Markowitz et al. 2000 0.021 0.0055 0.065 0.165 0.145 Stephens et al. 2004 0.014 0.0056 0.065 0.135 0.145 Hyroser et al. 2004 0.014 0.0056 0.035 0.7455 Vernier-Massouille et al. 2008 0.010 0.0042 0.024 0/ 839 Duricova et al. 2009 0.0096 0.0040 0.022 0 / 1.049 Jakobsen et al. 2009 0.010 0.0047 0.022 0 / 1.049 Jakobsen et al. 2010 0.011 0.0055 0.021 0 / 1.137 Keisen et al. 2011 0.011 0.0055 0.021 0 / 1.337 Ashworth et al. 2011 0.011 0.0055 0.021 0 / 1.337 Ashworth et al. 2012 0.0093 0.0051 0.015 0.12, 428 Kierkus et al. 2012 0.0093 0.0051 0.015 0 / 2.423		weight
Gryboski et al. 1994 0.024 0.0049 0.11 0 / 67 Markowitz et al. 2000 0.020 0.0056 0.085 0 / 145 Stephens et al. 2003 0.016 0.0056 0.043 0 / 227 de Ridder et al. 2008 0.0110 0.0056 0.032 0 / 445 Vermier-Massouile et al. 2008 0.0110 0.0042 0.022 0 / 733 Duricova et al. 2009 0.0096 0.0041 0.022 0 / 7145 Jakobsen et al. 2009 0.0096 0.0041 0.022 0 / 1.058 Ruemmele et al. 2009 0.010 0.0047 0.022 0 / 1.058 Ruemmele et al. 2010 0.011 0.0055 0.021 0 / 1.257 Hylams et al. 2011 0.0111 0.0056 0.021 0 / 1.257 Hylams et al. 2012 0.0096 0.0051 0.018 0 / 2.232 Hylams et al. 2012 0.0087 0.0048 0.017 0 / 2.232 Hyams et al. 2012 0.0087 0.0048 0.015 0 / 2.420 Kierkus et al. 2013		2.75
Lañgholz et al. 1997 0.024 0.0056 0.089 0/90 Markowiz et al. 2003 0.016 0.0056 0.045 0/145 Stephens et al. 2004 0.016 0.0056 0.045 0/257 Hyams et al. 2007 0.014 0.0056 0.045 0/257 Hyams et al. 2009 0.016 0.0056 0.024 0/257 Hyams et al. 2009 0.0089 0.0040 0.022 0/621 Hyams et al. 2009 0.010 0.0047 0.022 0/1098 Viola et al. 2009 0.011 0.0047 0.022 0/1.098 Viola et al. 2009 0.011 0.0047 0.022 0/1.098 Viola et al. 2009 0.011 0.0055 0.021 0/1.237 Grombé et al. 2011 0.011 0.0055 0.021 0/1.317 Kelsen et al. 2011 0.011 0.0055 0.021 0/1.317 Kelsen et al. 2011 0.011 0.0055 0.021 0/1.317 Kelsen et al. 2012 0.0086 0.0048 0.016 0.0048 Nature et al. 2011 0.011 0.0055 0.022 0/1.317 Kelsen et al. 2011 0.011 0.0055 0.024 0/1.317 Kelsen et al. 2011 0.011 0.0055 0.024 0/1.317 Kelsen et al. 2012 0.0087 0.0048 0.015 0/2.486 Assa et al. 2013 0.0079 0.0048 0.015 0/2.486 Assa et al. 2013 0.0079 0.0048 0.015 0/2.588 Navas-Lopez et al. 2013 0.0079 0.0044 0.013 1/3.422 Nut et al. 2014 0.0079 0.0047 0.013 1/3.429 Hyams et al. 2017 0.0058 0.0047 0.013 1/3.439 Hyams et al. 2017 0.0058 0.0047 0.013 1/3.439 Hyams et al. 2017 0.0056 0.0047 0.011 3/7.480 Choi et al. 2018 0.0076 0.0047 0.011 3/7.480 Choi et al. 2018 0.0076 0.0044 0.013 1/3.439 Hyams et al. 1996 0.012 0.0034 0.011 3/7.480 Verall 0.0076 0.0034 0.017 1/2.821 Hamber Devel diseases (no distinction steven Crohn's disease and ulcerative colitis) Markowiz et al. 1993 0.0017 0.0045 0.024 0/11 Markowiz et al. 1993 0.0017 0.0045 0.021 0/1.338 Vahabnezhad et al. 2012 0.0034 0.0017 1/2.821 Hamber	•	5.52 8.34
Stephens et al. 2003 0.016 0.0056 0.0445 0./257 Hyams et al. 2007 0.014 0.0056 0.036 0.7369 de Ridder et al. 2008 0.013 0.0050 0.032 0./435 Vernier-Massoulle et al. 2008 0.010 0.0042 0.022 0./633 Duricova et al. 2009 0.0066 0.0041 0.022 0./124 Hyams et al. 2009 0.0110 0.0042 0.022 0./1.098 Vicioa et al. 2009 0.0111 0.0055 0.022 0./1.137 Crombé et al. 2011 0.0111 0.0055 0.021 0./1.237 Astworth et al. 2011 0.0111 0.0055 0.021 0./1.317 Kelsen et al. 2011 0.0111 0.0055 0.021 0./1.337 Astworth et al. 2012 0.0096 0.0061 0.017 0./2.223 Hyams et al. 2011 0.0111 0.0055 0.021 0./1.337 Astworth et al. 2012 0.0096 0.00415 0./2.426 Hyams et al. 2013 0.0067 0.0046 0.015 0./2.664 Peneau et al. 2013 0.0076	•	11.13
de Ridder et al. 2007 0.014 0.0051 0.036 0.7369 de Ridder et al. 2008 0.013 0.0051 0.032 0.7483 Vernier-Massoullie et al. 2009 0.0096 0.0042 0.0224 0.7839 Jumicova et al. 2009 0.0096 0.0047 0.022 0.7921 Jumicova et al. 2009 0.010 0.0047 0.022 0.7138 Jumicova et al. 2009 0.011 0.0052 0.022 0.7137 Sinitsky et al. 2010 0.0111 0.0052 0.022 0.7137 Crombe et al. 2011 0.0111 0.0055 0.020 0.71,337 Ashworth et al. 2011 0.0111 0.0055 0.020 0.71,337 Ashworth et al. 2012 0.0093 0.0051 0.018 0.72,232 Hyams et al. 2012 0.0087 0.0048 0.015 0.72,486 Assa et al. 2013 0.0086 0.0045 0.013 1.3,5042 Hyams et al. 2012 0.0087 0.0046 0.013 1.3,4342 Paras et al. 2013 0.0076 0.0045 0.013 1.3,4342 Promery et al. 2015	►	13.96
Hyams et al. 2007 0.014 0.0051 0.036 0./369 Vernier-Massoullie et al. 2008 0.013 0.0042 0.024 0./435 Vernier-Massoullie et al. 2009 0.0096 0.0041 0.022 0./435 Jakobsen et al. 2009 0.0096 0.0041 0.022 0./1081 Hyams et al. 2009 0.010 0.0047 0.022 0./1081 Vicia et al. 2009 0.011 0.0047 0.022 0./1081 Scripty et al. 2011 0.011 0.0055 0.023 0./1137 Scripty et al. 2011 0.011 0.0055 0.021 0./1337 Ashworth et al. 2012 0.0096 0.0051 0.018 0./21232 Hyams et al. 2012 0.0087 0.0048 0.015 0./2486 Assa et al. 2013 0.0087 0.0048 0.015 0./2588 Navas-López et al. 2013 0.0085 0.0048 0.015 0./2588 Navas-López et al. 2013 0.0076 0.0047 0.013 1./3422 Hyams et al. 2017 0.0086 0.0047 0.013 1./3442 Hyams et al. 201	P-	16.79
de Ridder et al. 2008 0.013 0.0050 0.032 0/435 Uvernier-Massouille et al. 2009 0.0096 0.0042 0.022 0/839 Duricova et al. 2009 0.0089 0.0040 0.022 0/1049 Jakobsen et al. 2009 0.010 0.0047 0.022 0/1.049 Jakobsen et al. 2009 0.011 0.0057 0.022 0/1.137 Combé et al. 2011 0.011 0.0055 0.021 0/1.237 Hyams et al. 2011 0.011 0.0055 0.021 0/1.317 Keisen et al. 2011 0.0111 0.0055 0.021 0/1.317 Keisen et al. 2012 0.0063 0.0046 0.017 0/2.123 De Greef et al. 2012 0.0087 0.0048 0.015 0/2.486 Assa et al. 2013 0.0085 0.0048 0.015 0/2.486 Assa et al. 2013 0.0079 0.0046 0.013 1/3.142 Vuti et al. 2014 0.0076 0.0047 0.013 1/3.439 Hyams et al. 2017 0.0066 0.0047 0.013 1/3.439 Hyams et al. 2017 0.0		19.60 22.43
Vernier-Massouille et al. 2008 0.010 0.0042 0.022 0/123 Duricova et al. 2009 0.0086 0.0041 0.022 0/121 Hyams et al. 2009 0.010 0.0047 0.022 0/149 Jakobsen et al. 2009 0.011 0.0047 0.022 0/1198 Viola et al. 2010 0.011 0.0055 0.023 0/11257 Grambet et al. 2011 0.011 0.0055 0.023 0/11377 Crombet al. 2011 0.011 0.0056 0.021 0/13377 Ashworth et al. 2012 0.0086 0.0041 0.118 0/2.128 Perseer et al. 2012 0.0087 0.0048 0.015 0/2.486 Asas et al. 2013 0.0089 0.0051 0.015 0/2.486 Asas et al. 2013 0.0089 0.0047 0.013 1/3.342 Writ et al. 2014 0.0076 0.0047 0.013 1/3.422 Writ et al. 2014 0.0076 0.0047 0.013 1/3.432 Fumery et al. 2015 0.0076 0.004		25.26
Hyams et al. 2009 0.0089 0.0040 0.022 0 / 1.049 Jakobsen et al. 2009 0.010 0.0047 0.022 0 / 1.058 Ruemmele et al. 2009 0.011 0.0052 0.022 0 / 1.121 Sinitsky et al. 2010 0.011 0.0055 0.022 0 / 1.127 Crombé et al. 2011 0.011 0.0055 0.020 0 / 1.317 Keisen et al. 2011 0.011 0.0055 0.020 0 / 1.317 Keisen et al. 2012 0.0083 0.0061 0.018 0 / 2.232 Hyams et al. 2012 0.0087 0.0048 0.016 0 / 2.420 Kierkus et al. 2012 0.0087 0.0048 0.015 0 / 2.488 Assa et al. 2013 0.0089 0.0046 0.013 1 / 3.472 Peneau et al. 2013 0.0076 0.0046 0.013 1 / 3.472 Fummery et al. 2017 0.0086 0.0047 0.013 1 / 3.472 Fummery et al. 2017 0.0086 0.0047 0.013 1 / 3.472 Fummery et al. 2017 0.0086 0.0047 0.013 1 / 3.472 Fumery et al	•	28.10
Jákobsen et al. 2009 0.010 0.0049 0.021 0/1.058 Ruemmele et al. 2009 0.011 0.0052 0.022 0/1.121 Sinitsky et al. 2010 0.011 0.0055 0.022 0/1.137 Crombé et al. 2011 0.011 0.0055 0.021 0/1.337 Kelsen et al. 2011 0.011 0.0055 0.021 0/1.337 Ashworth et al. 2012 0.093 0.0051 0.017 0/2.323 Hyams et al. 2012 0.0087 0.0048 0.016 0/2.420 Kierkus et al. 2013 0.0087 0.0048 0.015 0/2.486 Assa et al. 2013 0.0087 0.0049 0.015 0/2.486 Assa et al. 2013 0.0079 0.0046 0.013 1/3.142 Nuti et al. 2014 0.0079 0.0047 0.013 1/3.242 Nuti et al. 2014 0.0076 0.0045 0.013 1/3.412 Pumers et al. 2013 0.0076 0.0047 0.013 1/3.422 Nuti et al. 2014 0.0076 0.0045 0.010 1/7.486 Maliet et al. 2014 0.00667	•	30.94
Ruemmele et al. 2009 0.010 0.0049 0.021 0/1,121 Sintisky et al. 2010 0.0111 0.0057 0.022 0/1,121 Crombé et al. 2011 0.0111 0.0055 0.020 0/1,137 Crombé et al. 2011 0.011 0.0055 0.020 0/1,337 Kelsen et al. 2011 0.0111 0.0055 0.020 0/1,337 Ashworth et al. 2012 0.0086 0.0051 0.018 0/2,128 De Greef et al. 2012 0.0087 0.0044 0.016 0/2,420 Kierkus et al. 2013 0.0085 0.0044 0.015 0/2,486 Assa et al. 2013 0.0079 0.0044 0.015 0/2,486 Assa et al. 2013 0.0079 0.0047 0.013 1/3,420 Nut et al. 2014 0.0079 0.0045 0.013 1/3,421 Humery et al. 2015 0.0076 0.0045 0.013 1/3,422 Wing et al. 2016 0.0075 0.0011 3/7,480 Malet et al. 2017 0.0066 0.0039 0.011 <t< td=""><td></td><td>33.77</td></t<>		33.77
Viola et al. 2009 0.011 0.0052 0.022 0/1,121 Sinisky et al. 2010 0.011 0.0055 0.021 0/1,257 Hyams et al. 2011 0.011 0.0055 0.021 0/1,337 Kelsen et al. 2011 0.011 0.0059 0.021 0/1,337 Ashworth et al. 2012 0.0093 0.0051 0.017 0/2,232 Hyams et al. 2012 0.0087 0.0049 0.015 0/2,486 Assa et al. 2013 0.0087 0.0049 0.015 0/2,588 Navas-López et al. 2013 0.0089 0.0051 0.015 0/2,604 Peneau et al. 2013 0.0079 0.0047 0.013 1/3,342 Nuti et al. 2014 0.0079 0.0047 0.013 1/3,443 Hyams et al. 2017 0.0066 0.0040 0.011 3/7,486 Mailet et al. 2018 0.0067 0.0041 0.011 3/7,486 Mailet et al. 2017 0.0066 0.0040 0.011 3/7,490 Choi et al. 2018 0.0064 0.0033 0.113 3/8,404 verall 0.0064 0.0		36.50 39.31
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flammatory bowel diseases (no distinction etween Crohn's disease and ulcerative colitis) Markowitz et al. 1993 0.0030 0.00019 0.046 0 / 165		100.00
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between Crohn's disease and ulcerative colitis) Markowitz et al. 1993 0.0030 0.00019 0.046 0 / 165		
	-	23.25
	+	46.49
Chouliaras et al. 2010 0.0059 0.0012 0.029 0 / 308		69.60
Colletti et al. 2013 0.0022 0.00031 0.015 1 / 4,651	t	100.00
verall 0.0022 0.00031 0.015 1 / 4,651		
	.00 0.50 1.00	

Crohn's disease; regression coefficient 0.00040, 95% CI 0.00035-0.00045 (*P* <0.0001) Ulcerative colitis; regression coefficient 0.00029, 95% CI 0.00016-0.00042 (*P* <0.0001) Inflammatory bowel disease (no distinction between Crohn's disease and ulcerative colitis); regression coefficient 0.00023, 95% CI 0.00021-0.00025 (*P* = 0.00039) Overall; regression coefficient 0.00031, 95% CI 0.00028-0.00034 (*P* <0.0001)

Figure 11. (Continued)

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Excluded article name				Rat	te ratio (95%	6 CI) with stud	y removed
Crohn's disease	Point	Lower limit	Upper limit				
Jess et al. 2013	2.47	1.90	3.20			-	
Peneau et al. 2013	2.41	1.89	3.08				
Kappelman et al. 2014	2.48	1.85	3.32			+	
Malham et al. 2019	2.28	1.66	3.13			-	
Overall	2.42	1.90	3.06			•	
Ulcerative colitis							
Jess et al. 2013	2.29	1.83	2.87				
Peneau et al. 2013	2.01	1.45	2.80				
Kappelman et al. 2014	2.13	1.14	3.99				
Malham et al. 2019	1.87	1.11	3.17				
Overall	2.10	1.51	2.90			•	
Inflammatory bowel diseases (no distinction between Crohn's disease and ulcerative colitis)							
Coletti et al. 2013 (anti-TNF alpha exposed)	2.74	1.61	4.69				
Coletti et al. 2013 (non biologic therapies)	2.86	1.63	5.02				
Hyams et al. 2017	4.90	2.08	11.53				+
Overall	3.04	1.88	4.92			-	
				0.01	0.1	1	10 100
			Risk	higher amo	ong control	Risk	higher among

Figure 12. A, Influence analysis of the overall risk of cancers reported as SIR among patients with pediatric IBD. **B**, Influence analysis of incident rates of overall risk of cancers among patients with pediatric IBD. **C**, Influence analysis of the risk of CRC among patients with pediatric IBD. **D**, Influence analysis of the risk of hematologic cancers among patients with pediatric IBD. **E**, Influence analysis of the risk of Hodgkin lymphoma among patients with pediatric IBD. **F**, Influence analysis of the risk of non-Hodgkin lymphoma among patients of the risk of the risk of non-Hodgkin lymphoma among patients with pediatric IBD. **G**, Influence analysis of the risk of leukemia among patients with pediatric IBD.

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Excluded article name		1	Una	Event rate (95% CI) with stud	ly removed
Crohn's disease	Point	Lower limit	Upper limit		
Weedon et al. 1973 Postuma et al. 1985 Verhave et al. 1990 Gold et al. 1993 Gryboski et al. 1994 Langholz et al. 1997 Markowitz et al. 2000 Stephens et al. 2000 de Ridder et al. 2003 de Ridder et al. 2007 de Ridder et al. 2007 de Ridder et al. 2009 Uriciova et al. 2009 Hyams et al. 2009 Hyams et al. 2009 Viola et al. 2010 Simitsky et al. 2010 Simitsky et al. 2011 Hyams et al. 2011 Kelsen et al. 2011 Kelsen et al. 2012 Kjerkus et al. 2012 Kjerkus et al. 2012 Kjerkus et al. 2013 Jess et al. 2013 Peneau et al. 2013 Peneau et al. 2014 Vahabnezhad et al. 2014 Fumery et al. 2014 Vahabnezhad et al. 2014 Fumery et al. 2017 Mallet et al. 2017	$\begin{array}{c} 0.013\\ 0.013\\ 0.014\\ 0.014\\ 0.014\\ 0.014\\ 0.014\\ 0.014\\ 0.014\\ 0.014\\ 0.014\\ 0.014\\ 0.014\\ 0.014\\ 0.014\\ 0.014\\ 0.014\\ 0.0014\\ 0.0014\\ 0.0014\\ 0.0014\\ 0.0014\\ 0.0014\\ 0.013\\ 0.0$	0.0081 0.0085 0.0086 0.0086 0.0086 0.0086 0.0088 0.0088 0.0088 0.0088 0.0088 0.0088 0.0088 0.0085 0.0086 0.0086 0.0086 0.0088 0.0086 0.0088 0.0086 0.0088 0.00	$\begin{array}{c} 0.021\\ 0.021\\ 0.021\\ 0.021\\ 0.021\\ 0.022\\ 0.022\\ 0.022\\ 0.022\\ 0.022\\ 0.022\\ 0.022\\ 0.022\\ 0.022\\ 0.022\\ 0.022\\ 0.022\\ 0.021\\ 0.022\\ 0.021\\ 0.022\\ 0.$		
Ölen et al. 2017 Choi et al. 2018 Turner et al. 2018 Malham et al. 2019 Overall	0.013 0.014 0.015 0.014 0.014	0.0080 0.0087 0.0093 0.0085 0.0087	0.020 0.022 0.023 0.022 0.021		
Ulcerative colitis					
Ladd et al. 1935 Korelitz et al. 1962 Skyring et al. 1965 Devroede et al. 1971 Patterson et al. 1971 Michener et al. 1979 Verhave et al. 1990 Gold et al. 1993 Hyams et al. 1996 Langholz et al. 1997 Jakobsen et al. 2009 Hyams et al. 2010 Kelsen et al. 2011 Jess et al. 2013 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017 Olen et al. 2019 Overall	0.030 0.029 0.030 0.027 0.030 0.031 0.030 0.032 0.032 0.032 0.030 0.032 0.032 0.030 0.029 0.032 0.031 0.028 0.036 0.028	0.018 0.016 0.017 0.015 0.017 0.018 0.017 0.019 0.018 0.018 0.018 0.018 0.017 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.018 0.017	0.052 0.050 0.052 0.047 0.051 0.053 0.051 0.055 0.054 0.052 0.054 0.055 0.054 0.055 0.054 0.055 0.054 0.055 0.055 0.056 0.055 0.055 0.052		
Inflammatory bowel diseases (no distinction between Crohn's disease and ulcerative co					
Markowitz et al. 1993	0.0079	0.0015	0.041	+	
Lee et al. 2005	0.0074	0.0014	0.039	<u>†</u>	
Chouliaras et al. 2010	0.0048	0.0008	0.026		
Colletti et al. 2013	0.017	0.011	0.027		
El-Matary et al. 2020	0.0046	0.0010	0.022		

Figure 12. (continued)

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Excluded article name		1	Una	Event rate (95% CI) w	ith study removed
Crohn's disease	Point	Lower limit	Upper limit		
Weedon et al. 1973	0.0070	0.0046	0.011	+ I	
Postuma et al. 1985	0 0074	0.0048	0.011		
Verhave et al. 1990 Gold et al. 1993	0.0073 0.0073	0.0048 0.0048	0.011 0.011	-	
Gillen et al. 1994	0.0067	0.0045	0.010		
Gryboski et al. 1994 Langholz et al. 1997	0.0074 0.0074	0.0048 0.0048	0.011 0.011	-	
Markowitz et al. 2000	0.0075	0.0049	0.011		
Stephens et al. 2003 de Ridder et al. 2004	0.0075 0.0074	0.0049 0.0048	0.012 0.011	-	
Hyams et al. 2007	0.0076	0.0049	0.012		
dé Ridder et al. 2008 Vernier-Massouille et al. 2008	0.0075 0.0078	0.0049 0.0051	0.012 0.012 0.012 0.012	-	
Duricova et al. 2009	0.0075	0.0049	0.012		
Hyams et al. 2009 Jakobsen et al. 2009	0.0076 0.0072	0.0049 0.0047	0.012 0.011	•	
Ruemmele et al. 2009 Viola et al. 2009	0.0074 0.0074	0.0048	0.011 0.011		
Pigneur et al. 2010	0.0074	0.0048 0.0047	0.011	•	
Siñitsky et al. 2010	0.0073	0.0048	0.011 0.012		
Crombé et al. 2011 Hyams et al. 2011	0.0076 0.0075	0.0049 0.0049	0.011		
Kélsen et al. 2011 De Greef et al 2012	0.0073 0.0076	0.0048 0.0049	0.011 0.012		
Hyams et al. 2012	0.0076	0.0050	0.012 0.012 0.012		
Kíerkus et al. 2012 Assa et al. 2013	0.0075 0.0076	0.0049 0.0049	0.012 0.012		
Navas-López et al. 2013	0.0073	0 0048	0.011		
Peneau et al. 2013	0.0078 0.0075	0.0051	0.012 0.012	·	
Nuti et al. 2014 Rosh et al. 2014	0.0076	0.0049 0.0050	0.012 0.012 0.012		
Vahabnezhad et al. 2014 Fumery et al. 2015	0.0076 0.0074	0.0050 0.0048	0.012 0.011	-	
Hvams et al. 2017	0.0080	0.0054	0.012		
Mallet et al. 2017 Olén et al. 2017	0.0072 0.0078	0.0047 0.0050	0.011 0.012		
Choi et al. 2018	0.0074	0.0048	0.011		
Turner et al. 2018 Malham et al. 2019	0.0079 0.0084	0.0052	0.012		
Olén et al. 2020	0.0079	0.0056 0.0051	0.013 0.012		
Overall	0.0075	0.0049	0.011		
Ulcerative colitis					
Ladd et al. 1935	0.019	0.011	0.034	-	
Lagercrantz et al. 1955	0.019	0.011	0.033		
Holowach et al. 1956	0.018	0.011	0.032		
Michener et al. 1961	0.018	0.011	0.027		
Hijmans et al. 1962 Korelitz et al. 1962	0.020 0.019	0.012 0.012	0.035 0.034	-	
Skyring et al. 1965	0.020	0.012	0.034	-	
Patterson et al. 1971	0.020	0.011	0.034	-	
Binder et al. 1973	0.020	0.012	0.035	-	
Michener et al. 1979	0.020	0.011	0.034	-	
Verhave et al. 1990	0.020	0.011	0.034		
Ahsgren et al. 1993	0.020	0.012	0.035		
Gold et al. 1993 Hyams et al. 1996	0.019 0.020	0.011 0.012	0.033 0.035	-	
Langholz et al. 1997	0.020	0.012	0.035	-	
Falcone et al. 2000	0.020	0.012	0.035	•	
Gower-Rousseau et al. 2009	0.021	0.012	0.035	•	
Jakobsen et al. 2009	0.019	0.011	0.034	•	
Hyams et al. 2010	0.020	0.012	0.035		
Kelsen et al. 2011	0.019	0.011	0.033		
Peneau et al. 2013 Vahabnezhad et al. 2014	0.021 0.020	0.012 0.012	0.036 0.035		
Hyams et al. 2017	0.020	0.012	0.035		
Olén et al. 2017	0.022	0.010	0.038	• 1	
Malham et al. 2019	0.023	0.014	0.038	•	
Olén et al. 2020	0.021	0.012	0.037	•	
Overall	0.020	0.012	0.034	•	
Inflammatory bowel diseases (no distin between Crohn's disease and ulcerativ					
Markowitz et al. 1993	0.0020	0.00011	0.035		
Lee et al. 2005	0.0020	0.00011	0.035		
Chouliaras et al. 2010	0.0012	0.00012	0.011	[
Offodilaras et al. 2010		0.00110	0.029	- F	1
Colletti et al. 2013	0.0059	0.00119	0.029		
	0.0059 0.0022	0.00119 0.00028	0.023	►	

Figure 12. (continued)

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Upper limit 0.0083 0.0087 0.0087 0.0089 0.0091 0.0092 0.0093 0.0094 0.0093 0.0093 0.0093 0.0093 0.0093 0.0093 0.0093 0.0093 0.0093 0.0093 0.0093 0.0094 0.0093 0.0093 0.0093 0.0093 0.0094 0.0093 0.0094 0.0093 0.0094 0.0093 0.0094 0.0093 0.0094 0.0093 0.0094 0.0093 0.0094 0.0093 0.0094 0.0093 0.0094 0.0093 0.0094 0.0093 0.0094		
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Figure 12. (continued)

Risk of Cancers in Patients with Pediatric Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis 117.e28

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		1		Event rate (95% CI) with study removed	
rohn's disease	Point	Lower limit	Upper limit		
Verhave et al. 1990 Gold et al. 1993	0.0058 0.0059	0.0035 0.0035	0.010 0.010	t	
Gryboski et al. 1994	0.0061	0.0036	0.010		
Langholz et al. 1997 Markowitz et al. 2000	0.0060 0.0061	0.0036	0.010 0.010		
Stephens et al. 2003 de Ridder et al. 2004	0.0062	0.0037 0.0037	0.010		
de Ridder et al. 2004 Hyams et al. 2007	0.0060 0.0063	0.0036 0.0037	0.010 0.010		
de Ridder et al. 2008	0.0062	0.0037	0.010		
Vernier-Massouille et al. 2008 Duricova et al. 2009	0.0064 0.0062	0.0039 0.0037	0.011 0.010		
Hyams et al. 2009	0.0061	0.0037	0.010		
Jåkobsen et al. 2009 Ruemmele et al. 2009	0.0057 0.0061	0.0035 0.0036	0.0090 0.010		
Viola et al. 2009	0.0060 0.0059	0.0036 0.0035	0.010		
Sinitsky et al. 2010 Crombé et al. 2011	0.0063	0.0037	0.010 0.010		
Hyams et al. 2011 Kelsen et al. 2011	0.0061 0.0059	0.0037 0.0036	0.010 0.010		
Ashworth et al. 2012	0.0065	0.0039	0.011		
De Greef et al 2012 Hyams et al. 2012	0.0062 0.0063	0.0037 0.0038	0.010 0.011		
Kierkus et al. 2012	0.0062	0.0037	0.010		
Assa et al. 2013 Navas-López et al. 2013	0.0062 0.0059	0.0037 0.0035	0.010 0.010		
Peneau et al. 2013	0.0064	0.0039	0.011		
Nuti et al. 2014 Rosh et al. 2014	0.0062 0.0063	0.0037 0.0038	0.010 0.011	·	
Fumery et al. 2015 Hyams et al. 2017	0.0060 0.0063	0.0036 0.0040	0.010 0.010		
Mallet et al. 2017	0.0056	0.0034	0.0090		
Choi et al. 2018 Fang et al. 2018	0.0060 0.0061	0.0036 0.0036	0.010 0.010		
Turner et al. 2018 Malham et al. 2019	0.0065 0.0069	0.0039 0.0043	0.011 0.011		
verall	0.0061	0.0037	0.010	·	
Icerative colitis					
Ladd et al. 1935	0.0071	0.0028	0.018	-	
Korelitz et al. 1962	0.0078	0.0031	0.020	•	
Skyring et al. 1965	0.0076	0.0030	0.019	• I I	
Patterson et al. 1971	0.0073	0.0029	0.018	• I I	
Verhave et al. 1990	0.0066	0.0027	0.016	• I I	
Gold et al. 1993	0.0063	0.0026	0.015	• I I	
Hyams et al. 1996	0.0079	0.0031	0.020	- I I	
Langholz et al. 1997	0.0076	0.0030	0.019	- I I	
Jakobsen et al. 2009	0.0075	0.0030	0.019	• I I	
Hyams et al. 2010	0.0074	0.0029	0.019	- I I	
Kelsen et al. 2011	0.0063	0.0026	0.015	• I I	
Ashworth et al. 2012	0.0084	0.0033	0.021	• I I	
Peneau et al. 2013	0.0079	0.0031	0.020	•	
Vahabnezhad et al. 2014	0.0072	0.0029	0.018	▶	
Hyams et al. 2017	0.0087	0.0036	0.021	▶	
Fang et al. 2018	0.0063	0.0026	0.015	▶	
Malham et al. 2019	0.0092	0.0042	0.020	▶	
verall	0.0074	0.0031	0.018	•	
nflammatory bowel diseases (no distinct between Crohn's disease and ulcerative of					
Markowitz et al. 1993	0.0022	0.00015	0.030		
Lee et al. 2005	0.0019	0.00014	0.024		
	0.0012	0.00016	0.008		
Chouliaras et al. 2010		0.0012	0.029	L	
Chouliaras et al. 2010 Colletti et al. 2013 Dverall	0.0059 0.0022	0.0012 0.00031	0.025	f l l	

Figure 12. (continued)

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Excluded article name				Event rate (95% CI) with study removed	
Crohn's disease	Point	Lower limit	Upper limit		
Verhave et al. 1990	0.0061 0.0062	0.0036 0.0036	0.010 0.011	t	
Gold et al. 1993 Gryboski et al. 1994	0.0062	0.0037	0.011	·	
Langholz et al. 1997 Markowitz et al. 2000	0.0063	0.0037	0.011		
Stephens et al. 2003	0.0064 0.0065	0.0037 0.0038	0.011 0.011	·	
de Ŕidder et al. 2004 Hyams et al. 2007	0.0063 0.0066	0.0037 0.0038	0.011 0.011		
de Ridder et al. 2008	0.0065	0.0038	0.011		
Vernier-Massouille et al. 2008 Duricova et al. 2009	0.0068 0.0065	0.0040 0.0038	0.012 0.011		
Hyams et al. 2009	0.0066	0.0038	0.011		
Jákobsen et al. 2009 Ruemmele et al. 2009	0.0061 0.0064	0.0036 0.0037	0.010 0.011	•	
Viola et al. 2009	0.0063 0.0062	0.0037 0.0036	0.011 0.011		
Sinitsky et al. 2010 Crombé et al. 2011 Hyams et al. 2011	0.0066	0.0038	0.011		
Hyams et al. 2011 Kelsen et al. 2011	0.0065 0.0062	0.0038 0.0037	0.011 0.011		
Ashworth et al. 2012	0.0069	0.0040	0.012		
De Greef et al 2012 Hyams et al. 2012	0.0066 0.0067	0.0038 0.0039	0.011 0.011	·	
Kierkus et al. 2012	0.0065 0.0066	0.0038 0.0038	0.011 0.011		
Assa et al. 2013 Navas-López et al. 2013 Peneau et al. 2013	0.0057	0.0034	0.009		
Peneau et al. 2013 Nuti et al. 2014	0.0068 0.0065	0.0040 0.0038	0.012 0.011	F	
Rosh et al. 2014	0.0067	0.0039	0.011		
Fumery et al. 2015 Hyams et al. 2017	0.0063 0.0073	0.0037 0.0045	0.011 0.012	•	
Mallet et al. 2017	0.0059	0.0035 0.0037	0.010		
Mallet et al. 2017 Choi et al. 2018 Fang et al. 2018	0.0063 0.0064	0.0037	0.011 0.011	·	
Turner et al. 2018 Malham et al. 2019	0.0069 0.0071	0.0040 0.0043	0.012 0.012		
Overall	0.0065	0.0038	0.011		
Ulcerative colitis					
Ladd et al. 1935	0.0069	0.0027	0.018		
Korelitz et al. 1962	0.0076	0.0029	0.020	•	
Skyring et al. 1965	0.0074	0.0028	0.019	•	
Patterson et al. 1971	0.0071	0.0027	0.018	- I I	
Verhave et al. 1990	0.0064	0.0025	0.016	•	
Gold et al. 1993	0.0061	0.0025	0.015		
Hyams et al. 1996	0.0077	0.0030	0.020	- I I	
Langholz et al. 1997	0.0074	0.0028	0.019	- I I	
Jakobsen et al. 2009	0.0073	0.0028	0.019		
Hyams et al. 2010	0.0072	0.0028	0.019	•	
Kelsen et al. 2011	0.0061	0.0025	0.015	•	
Ashworth et al. 2012	0.0082	0.0032	0.021	•	
Peneau et al. 2013	0.0077	0.0029	0.020		
Vahabnezhad et al. 2014	0.0070	0.0027	0.018		
Hyams et al. 2017	0.0087	0.0034	0.022		
Fang et al. 2018	0.0061	0.0025	0.015		
Malham et al. 2019	0.0090	0.0040	0.020		
Overall	0.0072	0.0029	0.018	ř	
Inflammatory bowel diseases (no dis between Crohn's disease and ulcerat colitis)					
Markowitz et al. 1993	0.0028	0.00010	0.073		
Lee et al. 2005	0.0025	0.000090	0.066	⊢	
Chouliaras et al. 2010	0.0012	0.00012	0.011		
Colletti et al. 2013	0.010	0.0021	0.046		
Overall	0.0030	0.00027	0.032		
				0.00 0.50 1.00	
				0.00 0.30 1.00	

Figure 12. (continued)

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		Lower	Uppor	Event rate (95% CI) with study removed		
rohn's disease	Point	Lower limit	Upper limit			
Verhave et al. 1990	0.0060	0.0036	0.010			
Gold et al. 1993 Gryboski et al. 1994	0.0061 0.0063	0.0037 0.0038	0.010 0.011			
Langholz et al. 1997	0.0062	0.0037	0.010	•		
Markowitz et al. 2000	0.0064	0.0038	0.011			
Stephens et al. 2003 de Ridder et al. 2004	0.0065 0.0063	0.0039 0.0037	0.011 0.010			
Hyams et al. 2007	0.0065	0.0039	0.011	•		
dé Ridder et al. 2008	0.0064	0.0038	0.011			
Vernier-Massouille et al. 2008 Duricova et al. 2009	0.0067 0.0065	0.0040 0.0039	0.011 0.011			
Hyams et al. 2009	0.0066	0.0039	0.011	•		
Jåkobsen et al. 2009 Ruemmele et al. 2009	0.0059 0.0063	0.0036 0.0038	0.010 0.011			
Viola et al. 2009	0.0062	0.0037	0.010	•		
Sinitsky et al. 2010 Crombé et al. 2011	0.0061 0.0066	0.0037 0.0039	0.010 0.011			
Hyams et al. 2011	0.0064	0.0039	0.011			
Kelsen et al. 2011	0.0062	0.0037	0.010	•		
Ashworth et al. 2012 De Greef et al 2012	0.0067 0.0065	0.0041 0.0039	0.011 0.011	i 1		
Hyams et al. 2012	0.0066	0.0040	0.011	• I		
Kíerkus et al. 2012	0.0064	0.0038	0.011	<u>t</u>		
Assa et al. 2013 Navas-López et al. 2013	0.0065 0.0061	0.0039 0.0037	0.011 0.010			
Peneau et al. 2013	0.0068	0.0041	0.011	•		
Nuti et al. 2014	0.0065	0.0039	0.011	:		
Rosh et al. 2014 Fumery et al. 2015	0.0066 0.0062	0.0040 0.0037	0.011 0.010	F		
Hvams et al. 2017	0.0079	0.0049	0.013	<u>•</u>		
Mallet et al. 2017 Choi et al. 2018	0.0057 0.0063	0.0035 0.0038	0.0093 0.011			
Turner et al. 2018	0.0067	0.0041	0.011	•		
verall	0.0064	0.0039	0.011	P		
Ladd et al. 1935 Korelitz et al. 1962	0.0072 0.0081	0.0031 0.0035	0.017 0.019			
Skyring et al. 1965	0.0078	0.0033	0.019	I I		
Patterson et al. 1971	0.0075	0.0032	0.017	I I		
Verhave et al. 1990	0.0067	0.0030	0.015	I I		
Gold et al. 1993	0.0062	0.0029	0.013	• I		
Hyams et al. 1996	0.0082	0.0035	0.019	• 1		
Langholz et al. 1997	0.0078	0.0033	0.018	• 1		
Jakobsen et al. 2009	0.0077	0.0033	0.018	• 1		
Hyams et al. 2010	0.0076	0.0032	0.018	• 1		
·	0.0062	0.0029	0.013	•		
Kelsen et al. 2011			0.010			
•	0.0087	0.0039	0.019			
Kelsen et al. 2011	0.0087 0.0082	0.0039 0.0035	0.019			
Kelsen et al. 2011 Ashworth et al. 2012 Peneau et al. 2013	0.0082	0.0035	0.019			
Kelsen et al. 2011 Ashworth et al. 2012 Peneau et al. 2013 Vahabnezhad et al. 2014	0.0082 0.0073	0.0035 0.0031	0.019 0.017			
Kelsen et al. 2011 Ashworth et al. 2012 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017	0.0082 0.0073 0.010	0.0035 0.0031 0.0048	0.019 0.017 0.021			
Kelsen et al. 2011 Ashworth et al. 2012 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017	0.0082 0.0073	0.0035 0.0031	0.019 0.017			
Kelsen et al. 2011 Ashworth et al. 2012 Peneau et al. 2013 Vahabnezhad et al. 2014	0.0082 0.0073 0.010	0.0035 0.0031 0.0048	0.019 0.017 0.021			
Kelsen et al. 2011 Ashworth et al. 2012 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017	0.0082 0.0073 0.010	0.0035 0.0031 0.0048	0.019 0.017 0.021			
Kelsen et al. 2011 Ashworth et al. 2012 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017	0.0082 0.0073 0.010 0.0076	0.0035 0.0031 0.0048	0.019 0.017 0.021			
Kelsen et al. 2011 Ashworth et al. 2012 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017 verall flammatory bowel diseases (no dist etween Crohn's disease and ulcerati	0.0082 0.0073 0.010 0.0076 inction ve colitis)	0.0035 0.0031 0.0048 0.0034	0.019 0.017 0.021 0.017			
Kelsen et al. 2011 Ashworth et al. 2012 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017 verall flammatory bowel diseases (no dist tween Crohn's disease and ulcerati Markowitz et al. 1993	0.0082 0.0073 0.010 0.0076 inction ve colitis) 0.0022	0.0035 0.0031 0.0048 0.0034 0.00015	0.019 0.017 0.021 0.017 0.017			
Kelsen et al. 2011 Ashworth et al. 2012 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017 verall flammatory bowel diseases (no dist stween Crohn's disease and ulcerati Markowitz et al. 1993 Lee et al. 2005	0.0082 0.0073 0.010 0.0076 inction ve colitis) 0.0022 0.0019	0.0035 0.0031 0.0048 0.0034 0.00015 0.00015	0.019 0.017 0.021 0.017 0.017			
Kelsen et al. 2011 Ashworth et al. 2012 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017 verall flammatory bowel diseases (no dist etween Crohn's disease and ulcerati Markowitz et al. 1993 Lee et al. 2005 Chouliaras et al. 2010	0.0082 0.0073 0.010 0.0076 inction ve colitis) 0.0022 0.0019 0.0012	0.0035 0.0031 0.0048 0.0034 0.00015 0.00015 0.00014 0.00016	0.019 0.017 0.021 0.017 0.017 0.030 0.030 0.024 0.0085			
Kelsen et al. 2011 Ashworth et al. 2012 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017 verall flammatory bowel diseases (no dist etween Crohn's disease and ulcerati Markowitz et al. 1993 Lee et al. 2005 Chouliaras et al. 2010 Colletti et al. 2013	0.0082 0.0073 0.010 0.0076 inction ve colitis) 0.0022 0.0019 0.0012 0.0059	0.0035 0.0031 0.0048 0.0034 0.00015 0.00015 0.00014 0.00016 0.0012	0.019 0.017 0.021 0.017 0.017 0.030 0.024 0.0085 0.029			
Kelsen et al. 2011 Ashworth et al. 2012 Peneau et al. 2013 Vahabnezhad et al. 2014 Hyams et al. 2017 verall flammatory bowel diseases (no dist etween Crohn's disease and ulcerati Markowitz et al. 1993 Lee et al. 2005 Chouliaras et al. 2010	0.0082 0.0073 0.010 0.0076 inction ve colitis) 0.0022 0.0019 0.0012	0.0035 0.0031 0.0048 0.0034 0.00015 0.00015 0.00014 0.00016	0.019 0.017 0.021 0.017 0.017 0.030 0.030 0.024 0.0085			

Figure 12. (Continued)

Table I. PubMed search strategy							
PubM	PubMed search strategy Number of studies						
#1	pediatric* [MeSH Terms] OR childhood [Text Word]	332 986					
#2	"inflammatory bowel diseases" [MeSH Terms] OR "Crohn's disease" [Text Word] OR "ulcerative colitis" [Text Word]	95 536					
#3	cancer* [Text Word] OR malignancy* [Text Word] OR "colorectal cancer*" [Text Word] OR "hematologic cancer*" [Text Word] OR "Hodgkin's lymphoma" [Text Word] OR "non Hodgkin's lymphoma" [Text Word] OR lymphoma [Text Word] OR leukemia [Text Word]	2 260 522					
#4	#1 OR #2 AND #3	39 169					

Table II. Risk of bias in RCTs of pediatric IBDs reporting the risk of cancers								
Authors	Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Hyams et al ¹¹	2007	?	-	-	-	-	-	-
Hyams et al ²⁶	2012	+	-	-	-	-	-	-
Markowitz et al ⁸	2000	+	?	?	?	+	-	-
Ruemmele et al ¹⁷	2009	+	-	-	-	+	-	-

A plus sign indicate low risk of bias. A question mark indicates unclear risk of bias. A minus sign indicate high risk of bias. Other bias includes the risk of bias due to conflict of interest (for example, authors employed by, held stock in, or received funds from manufacturer).

Table IV. Summary of findings with quality of the evidence (GRADE)

Bibliographies

Outcomes	No of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)
The risk of overall cancers reported as SIR among patients with pediatric IBD rate ratio	17 450(6 studies)	$\oplus \oplus \oplus \ominus Moderate^*$ due to large effect	RR 2.39 (2-2.86)
Incidence rates of overall cancers among pediatric IBD.pooled event rate	32 417(52 studies [†])	⊕ ⊖ ⊖ ⊖ Very low ^{‡,§,¶} due to risk of bias, inconsistency, publication bias	pooled event rate 0.018 (0.013- 0.025)
Incidence rates of CRC among pediatric IBD.pooled event rate	35 083 (60 studies**)	⊕ ⊖ ⊖ ⊖ Very low ^{11,41,§§} due to risk of bias, inconsistency, publication bias	pooled event rate 0.010 (0.0074- 0.014)
Incidence rates of hematologic cancers among pediatric IBDpooled event rate	31 477 (48 studies ^{¶¶})	⊕ ⊖ ⊖ ⊖ Very low ^{††,***,†††} due to risk of bias, inconsistency, publication bias	pooled event rate 0.0054 (0.0039- 0.0075)
Incidence rates of Hodgkin lymphoma among pediatric IBDpooled event rate	22 581 (44 studies ⁺⁺⁺)	$\oplus \ominus \ominus \ominus$ Very low ^{4.111} due to risk of bias, publication bias	pooled event rate 0.0061 (0.004- 0.093)
Incidence rates of non-Hodgkin lymphoma among pediatric IBDpooled event rate	22581 (44 studies ^{##+})	⊕ ⊖ ⊖ ⊖ Very low ^{‡.8§§} .¶¶ due to risk of bias, inconsistency, publication bias	pooled event rate 0.0065 (0.0041-0.01)
Incidence rates of leukemia among pediatric IBDpooled event rate	15876 (43 studies ⁺⁺⁺)	 ⊕ ⊖ ⊖ ⊖ Very low^{4,111} due to risk of bias, publication bias 	pooled event rate 0.0056 (0.0028- 0.011)

RR, risk ratio.

*The pooled SIR is 2.39.

†Nine prospective and 44 retrospective studies (1 study included both study designs) were included. Four RCTs were counted as prospective studies.

‡There were only 8 high quality papers included in this analysis.

§The heterogeneity was high: $l^2 = 89.10\%$.

There were small-study effects or publication biases as assessed by the Begg and Egger tests (P = .00072, .00060, respectively).

**Nine prospective and 52 retrospective studies (1 study included both study designs) were included. Four RCTs were counted as prospective studies.

††There were only 10 high quality papers included in this analysis.

‡‡The heterogeneity was high: $l^2 = 81.30\%$.

\$\$There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, = .013, respectively).

¶¶Nine prospective and 40 retrospective studies (1 study included both study designs) were included. Four RCTs were counted as prospective studies. ***The heterogeneity was moderate: ℓ^2 = 34.25%.

++++There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, <.0001, respectively).

¶¶¶There were small-study effects or publication biases as assessed by the Begg and Egger tests (P < .0001, < .0001, respectively).

	Subgroups	Numbers of included studies	95% CI of the regression coefficient	P value (for regression coefficient)	Residual error sums of squares (<i>Qe</i>)	P value (for <i>Qe</i>)
Overall cancers	CD	21	-0.0095 to 0.019	.26	12.05	.80
	UC	6	-0.037 to 0.018	.24	8.47	.13
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	27	-0.018 to 0.0048	.13	30.98	.15
CRC	CD	21	-0.011 to 0.026	.79	8.90	.94
	UC	7	-0.040 to 0.014	.17	4.77	.69
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	28	-0.020 to 0.0078	.19	20.17	.78
Hematologic cancers	CD	20	-0.029 to 0.014	.24	12.01	.68
	UC	6	-0.024 to 0.067	.82	0.53	.99
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	26	-0.022 to 0.017	.41	14.17	.90
Hodgkin lymphoma	CD	18	-0.024 to 0.023	.48	7.66	.91
	UC	6	-0.024 to 0.067	.82	0.53	.99
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	24	-0.017 to 0.026	.66	8.93	1.00
Non-Hodgkin lymphoma	CD	18	-0.031 to 0.013	.22	10.73	.71
	UC	6	-0.024 to 0.067	.82	0.53	.99
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	24	-0.023 to 0.017	.39	12.81	.92
Leukemia	CD	19	-0.023 to 0.024	.52	7.54	.91
	UC	6	-0.024 to 0.067	.82	0.53	.99
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	25	-0.016 to 0.026	.69	8.71	.99

 Table V. Results of meta-regression analyses of steroid as the concomitant medication and the risk of cancers among patients with IBDs

NA, not available.

	Subgroups	Numbers of included studies	95% CI of the regression coefficient	P value (for regression coefficient)	Residual error sums of squares (<i>Qe</i>)	<i>P</i> value (for <i>Qe</i>)
Overall cancers	CD	27	-0.014 to 0.026	71	13.83	.84
	UC	8	-0.011 to 0.034	.84	2.13	.71
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	35	-0.011 to 0.013	.58	18.38	.86
CRC	CD	27	-0.018 to 0.027	.66	10.35	.96
	UC	10	-0.010 to 0.034	.15	3.27	.77
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	37	-0.013 to 0.011	.46	16.66	.96
Hematologic cancers	CD	27	-0.015 to 0.026	.70	15.80	.73
	UC	9	-0.0014 to 0.055	.31	4.10	.54
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	36	-0.0046 to 0.026	.083	21.74	.75
Hodgkin lymphoma	CD	25	-0.022 to 0.027	.57	12.54	.86
	UC	8	-0.0014 to 0.055	.31	4.10	.54
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	33	-0.0068 to 0.027	.12	18.81	.84
Non-Hodgkin lymphoma	CD	25	-0.024 to 0.027	.54	15.13	.65
	UC	8	-0.0092 to 0.061	.075	4.09	.39
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	33	-0.010 to 0.025	.79	20.66	.66
Leukemia	CD	25	-0.023 to 0.026	.54	12.84	.85
	UC	8	-0.0013 to 0.055	.31	4.11	.53
	IBD (no distinction made between CD or UC)	NA	NA	NA	NA	NA
	Overall	33	-0.0079 to 0.026	.15	19.52	.81

Table VI. Results of meta-regression analyses of immunomodulator (thiopurine) as the concomitant medication and the risk of cancers among patients with IBDs

Table VII. Results of meta-regression analyses of antitumor necrosis factor agents as the concomitant medication and the risk of cancers among patients with IBDs

	Subgroups	Numbers of included studies	95% CI of the regression coefficient	<i>P</i> value (for regression coefficient)	Residual error sums of squares (<i>Qe</i>)	P value (for <i>Qe</i>)
Overall cancers	CD	28	-0.024 to 0.0022	.0052	12.46	.93
	UC	6	-0.025 to 0.018	.38	1.56	.46
	IBD (no distinction made between CD or UC)	1	NA	NA	NA	NA
	Overall	35	-0.021 to 0.00026	.22	15.69	.94
CRC	CD	28	-0.022 to 0.0076	.17	9.31	.99
	UC	6	-0.019 to 0.021	.54	2.76	.43
	IBD (no distinction made between CD or UC)	1	NA	NA	NA	NA
	Overall	35	-0.019 to 0.0026	.069	14.25	.98
Hematologic cancers	CD	28	-0.0093 to 0.029	.16	14.32	.86
	UC	7	-0.0033 to 0.046	.45	2.58	.46
	IBD (no distinction made between CD or UC)	1	NA	NA	NA	NA
	Overall	36	-0.0027 to 0.025	.057	18.46	.89
Hodgkin lymphoma	CD	26	-0.014 to 0.028	.73	11.28	.94
	UC	6	-0.0033 to 0.046	.45	2.58	.46
	IBD (no distinction made between CD or UC)	1	NA	NA	NA	NA
	Overall	33	-0.0049 to 0.024	.098	15.64	.94
Non-Hodgkin lymphoma	CD	26	-0.0095 to 0.029	.84	14.54	.80
	UC	6	-0.0053 to 0.049	.058	3.06	.38
	IBD (no distinction made between CD or UC)	1	NA	NA	NA	NA
	Overall	33	-0.0035 to 0.026	.067	19.15	.83
Leukemia	CD	26	-0.015 to 0.027	.72	11.51	.93
	UC	6	-0.0053 to 0.049	.058	3.06	.38
	IBD (no distinction made between CD or UC)	1	NA	NA	NA	NA
	Overall	33	-0.0064 to 0.025	.12	16.43	.93