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Malignancy and mortality in paediatric-onset inflammatory bowel disease: a 3-year prospective, multinational study from the paediatric IBD Porto group of ESPGHAN

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Summary

Background: Risk benefit strategies in managing inflammatory bowel diseases (IBD) are dependent upon understanding the risks of uncontrolled inflammation vs those of treatments. Malignancy and mortality in IBD have been associated with disease-related inflammation and immune suppression, but data are limited due to their rare occurrence.

Aim: To identify and describe the most common causes of mortality, types of cancer and previous or current therapy among children and young adults with paediatric-onset IBD.

Methods: Information on paediatric-onset IBD patients diagnosed with malignancy or mortality was prospectively collected via a survey in 25 countries over a 42-month period. Patients were included if death or malignancy occurred after IBD diagnosis but before the age of 26 years.

Results: In total, 60 patients were identified including 43 malignancies and 26 fatal cases (9 due to cancer). Main causes of fatality were malignancies (n = 9), IBD or IBD-therapy related nonmalignant causes (n = 10; including 5 infections), and suicides (n = 3). Three cases, all fatal, of hepatosplenic T-cell lymphoma were identified, all were biologic-naïve but thiopurine-exposed. No other haematological malignancies were fatal. The 6 other fatal cancer cases included 3 colorectal adenocarcinomas and 3 cholangiocarcinomas (CCAs). Primary sclerosing cholangitis (PSC) was present in 5 (56%) fatal cancers (1 colorectal carcinoma, 3 CCAs and 1 hepatosplenic T-cell lymphoma).

Conclusions: We report the largest number of paediatric-onset IBD patients with cancer and/or fatal outcomes to date. Malignancies followed by infections were the major causes of mortality. We identified PSC as a significant risk factor for cancer-associated mortality. Disease-related adenocarcinomas were a commoner cause of death than lymphomas.

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1 | INTRODUCTION

Inflammatory bowel diseases (IBD) are associated with a long list of both treatment and disease-related complications and cancer. Paediatric-onset IBD is characterised by more extensive and aggressive disease, a longer disease duration and a higher need for immune suppression early in the disease,[1,2] all of which may be risk factors for complications or cancer. Although immune suppression may be associated with malignancy, hemophagocytic lymphohistiocytosis and opportunistic infections, it may reduce the risk of fibrostricturing disease, surgery and disease-associated tumours such as bowel adenocarcinoma.[3-8] Combination therapy with other immunosuppressive medications may increase the treatment success of biologics but is associated with an increased risk of adverse events. Hyams et al[7] demonstrated that the standardised incidence ratio (SIR) for malignancy among 5766 paediatric-onset IBD patients included in the DEVELOP registry was significantly elevated for patients receiving combination therapy with thiopurine and biologics (SIR 3.06) but not with thiopurine or anti-tumour necrosis factor alpha (TNFα) as monotherapy. Several studies in adult IBD patients have shown that current exposure to thiopurines appeared to be more significantly associated with increased incidence of thiopurine-related malignancies than past exposure to thiopurines,[9] while the DEVELOP registry did not delineate treatment as current or past.[7]

Given the rarity of some of these events, more detailed information on paediatric-onset IBD patients who develop cancer or have a fatal outcome is needed to obtain more insight in predictive factors of severe outcomes and to be able to optimise evidence-based treatment guidelines. The aim of this study was to identify and describe the most common causes of mortality, types of cancer and previous or current therapy among children with paediatric-onset IBD. We also aimed to describe the patient-specific and disease-specific characteristics of these groups and investigate the relationship between severe outcomes in paediatric-onset IBD patients and treatment exposure.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a prospective multinational observational study performed in collaboration with the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). We collected patients at all sites in 25 countries for 42 months from June 2013 to December 2016 (Table S1 tabulates all participating countries). The study was conducted in all sites according to the instructions of the local ethical committees. Some committees waived the need for informed consent due to the anonymous and non-interventional fashion of the study.

In each participating country, both a paediatric gastroenterologist and an adult gastroenterologist were appointed as national representatives. The representative paediatric gastroenterologist contacted paediatric gastroenterologists in each country through e-mail every 6 months throughout the study period in an attempt to obtain all new cases of malignancy and/or mortality in patients with paediatric-onset IBD over the previous 6-month period. An explicit case report form (provided in Supporting Information) was completed by the reporting paediatric gastroenterologist for all newly reported cases, using data from individual patient records. Cases that occurred prior to the study period were not included in our study. Existing IBD or cancer registries were not used to identify cases. In order to assess response rates, paediatric gastroenterologists were asked to actively respond negatively if no case was identified. When data were unclear the paediatric gastroenterologist was queried further by e-mail. In order to identify cases that may have transitioned to adult care or developed malignancies after age 18 as a result of paediatric disease, the representative adult gastroenterologists followed the same procedures. Cases were ascertained by comparing and cross-checking all reported cases on country, year of reporting, sex and exact diagnosis.

Survey response rates per country were monitored throughout the study period to obtain insight into coverage (Table S1). Response rate was calculated as the number of physicians replying to the e-mail call out of the total number of registered paediatric or adult gastroenterologists contacted in that country. Additional e-mails were sent out by ESPGHAN to increase awareness among gastroenterologists. The European Crohn's and Colitis Organisation (ECCO) provided logistical support and invited national representatives to nominate national coordinators. In addition, national patient organisations were informed on the study and every year investigators meetings were organised with national representatives from all participating countries.

2.2 | Patient selection

Inclusion criteria for reported cases were patients with paediatric-onset IBD diagnosed according to the revised Porto criteria before 19 years of age,[10] who died or were diagnosed with a malignancy after IBD diagnosis but before the age of 26 years. Patients with IBD-like inflammation due to proven monogenetic defects were excluded. Although infections are usually due to current immune suppression, malignancies may develop later after transition to adult care. In almost all European countries, paediatric-onset IBD patients <16 years are cared for by paediatric gastroenterologists, and transition to adult care occurs after this age. As current guidelines for cancer surveillance in children and adults recommend surveillance starting from 8 to 10 years after disease-onset of paediatric-onset IBD, we extended follow-up to 10 years after the age of 16 years to capture paediatric-onset IBD patients who developed cancer or mortality after transition to adult care.

2.3 | Data collection

Data were collected by means of a case report form, which included 8 domains and 42 questions. The first 3 domains were divided into demographics, patient characteristics and disease characteristics, including questions on reporting physician, country, sex, IBD type, age at IBD diagnosis and comorbidities. The following domains of characteristics of malignancy and/or mortality included questions on

type of malignancy and/or cause of death, age at malignancy and/or death, and IBD disease duration. The last domain contained questions on current and past therapy exposure, including thiopurines, biologics (agents blocking TNFα) or other immunosuppressant drugs (steroids, methotrexate and calcineurin inhibitors), as well as exposure to combination therapies and duration of exposure. Current exposure was defined as exposure in the 3 months prior to malignancy diagnosis or fatal outcome. Past exposure was defined as exposure previous to the last 3 months. "Ever exposed" was defined as exposure at any time prior to the malignancy or fatal outcome. Data were stored in a central database in the Erasmus Medical Centre in Rotterdam, The Netherlands.

2.4 | Number of paediatric-onset IBD patients at risk (denominator)

Representative paediatric gastroenterologists of all European participating countries were requested to complete a survey that collected data stating which regions in their country as defined by the Nomenclature of Territorial Units for Statistics (NUTS) were covered during the years of data collection in this study (Table S2). Coverage was calculated for all European countries responding to the survey (Table S2). Full coverage was assumed for adults (20-26 years).

Eurostat most recent census data (2016) were used to obtain the total number of individuals covered in the general population (0-26 years) per country. This comprised the population from which the reported paediatric-onset IBD cases with cancer and/or mortality in our study were derived. In literature, paediatric-onset IBD prevalence among children (0-19 years) is around 30 per 100 000.[11-15] An estimated paediatric-onset IBD prevalence <26 years of 60 per 100 000 was used to calculate the number of paediatric-onset IBD patients at risk for all countries. As this prevalence is likely an overestimation of the real prevalence,[11-15] this is a conservative approach ensuring that the incidences of cancer and mortality in the paediatric-onset IBD patient population are not overestimated.

The total covered population (0-26 years) was multiplied by the estimated paediatric-onset IBD prevalence for this age group, resulting in an estimation of the true population that has the disease (number of paediatric-onset IBD patients 0-26 years at risk). As the study was conducted over 42 months, the number of paediatric-onset IBD patients at risk per year was multiplied by the years of exposure (3.5 patient-years).

TABLE 1 Malignancy incidence in paediatric-onset IBD patients <26 years in European countries

Country	No. malignancy cases reported	Paediatric-onset IBD patients in 3.5 years Denominator data[a]	Annual incidence per 1 000 000 patients[b]	No. of expected cases[c]	Variation from expected
Austria (AT)	0	5021	0	0.86	−0.86
Belgium (BE)	0	4056	0	0.69	−0.69
Croatia (HR)	1	2353	425	0.40	0.60
Czech Republic (CZ)	2	5866	341	1.01	0.99
Denmark (DK)	0	3737	0	0.64	−0.64
Finland (FI)	3	3356	894	0.57	2.43
France (FR)	4	44 016	91	7.54	−3.54
Greece (EL)	2	5800	345	0.99	1.01
Ireland (IE)	2	3460	578	0.59	1.41
Italy (IT)	3	12 834	234	2.20	0.80
Poland (PL)	0	21 957	0	3.76	−3.76
Portugal (PT)	0	5565	0	0.95	−0.95
Romania (RO)	0	11 332	0	1.94	−1.94
Sweden (SE)	3	6461	464	1.11	1.89
Switzerland (CH)	1	4118	243	0.71	0.29
Netherlands (NL)	6	10 722	560	1.84	4.16
UK—England	5	36 624	137	6.27	−1.27
UK—Scotland	1	3338	300	0.57	0.43
UK—Wales	0	2010	0	0.34	−0.34
Total	**33**	**192 625**	**171**	**33**	**NR**

IBD, inflammatory bowel disease; No, number of; NR, not relevant; UK, United Kingdom.
[a]See Table S2 for calculation of denominator data.
[b]Incidence calculation based on the number of patient-years and the number of reported cases. Incidence is reported in patient-years.
[c]The average incidence for all countries was used to calculate expected number of cases per country.

2.5 | Calculation of cancer and mortality incidence

Cancer and mortality incidences for paediatric-onset IBD patients <26 years were calculated based on the number of patient-years (as described above) and the number of reported cases per country and in total (Tables 1 and 2). Confidence intervals (CIs) were calculated using Byar's approximation based on a Poisson distribution. The relative risk (RR) and its 95% CI were calculated according to Altman, 1991, in order to compare cancer incidence in paediatric-onset IBD patients with the general population. The average incidence for all countries was used to calculate the expected number of cases per country according to their covered population (Tables 1 and 2, Figure 1). Poisson analysis was used to investigate the extent of variation in the number reported cases per country with statistical inference. Random-effects model for meta-analysis was used due to high heterogeneity in the results to investigate the incidences of cancer and/or mortality. The rare nature of the examined cases precluded comparisons between smaller regions and/or comparisons between sub-categories of the cases.

2.6 | Statistics

Data are presented as median and interquartile range (IQR) or percentages. Data analyses were performed using IBM SPSS version 24 (Armonk, NY, USA) and GraphPad Prism version 5.0 (San Diego, CA, USA). Baseline demographic and disease characteristics were evaluated for the entire cohort using descriptive statistics, including means and standard deviations (SD) or median and IQR for continuous variables, and frequencies and percentages for categorical outcomes. For comparison between 3 groups, the Fisher's exact test was used for categorical outcomes and the Kruskal-Wallis *H* test was used for continuous variables. If there was a statistically significant difference between the 3 groups, the Mann-Whitney test (continuous variables) or Fisher's exact test (categorical variables) was used to test differences between 2 groups as a follow-up analysis. *P* values <0.05 were considered to present a statistically significant difference. In case of multiple comparisons, an adjusted significance level was used according to the Bonferroni correction (significance level = 0.05/number of comparisons).

3 | RESULTS

3.1 | Coverage and participation response rates per country

Except for 3 countries, all European countries responding to the survey claimed full coverage (Table S2). Response rates differed between the 25 countries (Table S1). Data collection among paediatric gastroenterologists was high in 15 of 25 participating countries, with ≥70% of paediatric gastroenterologists responding to the semi-annual e-mails throughout the study period with a valid reply. Data collection from adult gastroenterologists had a ≥70% response rate in 9 of 25 countries respectively (Table S1).

3.2 | Patient characteristics

A total of 60 patients with either fatalities or cancer were identified during the study period (UC, n = 21; CD, n = 33; IBD-U, n = 6). Of the 60 patients, 43 were diagnosed with malignancy and in 26 a fatality occurred; in 9 (35%) of the latter the cause of death was cancer.

3.3 | Malignancy and mortality incidence

The final estimated number of paediatric-onset IBD patients aged 0-26 years at risk in Europe was 192 625 patient-years. Since 33 cancer cases were reported in 192 625 patient-years (Table 1), the cancer incidence in paediatric-onset IBD patients aged 0-26 years was 171 per 1 000 000 (95% CI 120-238). Based on literature from national cancer registries, the cancer incidence in the general population aged 0-26 years is estimated at 210 per 1 000 000.[16,17] Overall, the cancer incidence among paediatric-onset IBD patients was not found to be significantly different compared to the general population for this age group. The RR for malignancy in the paediatric-onset IBD population compared to the general population was found to be 0.816 (95% CI 0.57-1.18, $P = 0.277$). However, cancer incidences among paediatric-onset IBD patients in specific countries, including the Netherlands, Finland and Sweden, were higher compared to the general population (Table 1).

To obtain insight in under-reporting per country, reported number of cases were compared to the average of the reported rates (Tables 1 and 2, Figure 1A). Five countries were found to have significantly different (lower or higher) number of reported cases compared to the average of the reported rates (Figure 1B). A negative difference in variation was seen in France, Poland and Romania. Particularly, France and Poland reported a significantly lower number of cases than expected for both cancer and mortality ($P = 0.013$ and 0.024, respectively, based on a Poisson distribution) which indicated potential under-reporting. When excluding these 3 countries, the cancer incidence in paediatric-onset IBD patients aged 0-26 years increased to 230 per 1 000 000 (95% CI 157-326). Sweden, Finland and the Netherlands presented significantly more cases than expected ($P = 0.007$, 0.011 and 0.007 respectively).

3.4 | Malignancy

We identified 43 malignancies during the study period of which 24 (56%) occurred in patients with CD (Table 3). Patients who developed a fatal outcome due to their malignancy (6 males, 3 females) had been diagnosed with IBD at a median age of 12.9 year (IQR 8.3-15.4). They had significantly longer IBD disease duration to cancer than those with a nonfatal outcome (9.1 years [IQR 5.8-12.2] vs 4.3 years [IQR 2.0-9.0], $P = 0.019$) and developed cancer at a higher median age of 20.0 years (IQR 19.0-23.5)

TABLE 2 Mortality incidence in paediatric-onset IBD patients <26 years in European countries

Country	No. fatal cases reported[a]	Paediatric-onset IBD patients in 3.5 years Denominator Data[b]	Annual incidence per 1 000 000 patients[c]	No. of expected cases[d]	Variation from expected
Austria (AT)	0	5021	0	0.57	−0.57
Belgium (BE)	0	4056	0	0.46	−0.46
Croatia (HR)	1	2353	425	0.27	0.73
Czech Republic (CZ)	0	5866	0	0.67	−0.67
Denmark (DK)	0	3737	0	0.43	−0.43
Finland (FI)	2	3356	596	0.38	1.62
France (FR)	0	44 016	0	5.03	−5.03
Greece (EL)	0	5800	0	0.66	−0.66
Ireland (IE)	0	3460	0	0.40	−0.40
Italy (IT)	3	12 834	234	1.47	1.53
Poland (PL)	1	21 957	46	2.51	−1.51
Portugal (PT)	0	5565	0	0.64	−0.64
Romania (RO)	1	11 332	88	1.29	−0.29
Sweden (SE)	5	6461	774	0.74	4.26
Switzerland (CH)	1	4118	243	0.47	0.53
Netherlands (NL)	3	10 722	280	1.22	1.78
UK—England	5	36 624	137	4.18	0.82
UK—Scotland	0	3338	0	0.38	−0.38
UK—Wales	0	2010	0	0.23	−0.23
Total	**22**	**192 625**	**114**	**22**	**NR**

IBD, inflammatory bowel disease; No, number of; NR, not relevant; UK, United Kingdom.
[a]Including fatal cancer and mortality due to other causes.
[b]See Table S2 for calculation of denominator data.
[c]Incidence calculation based on the number of patient-years and the number of reported cases. Incidence is reported in patient-years.
[d]The average incidence for all countries was used to calculate expected number of cases per country.

vs 16.6 years (IQR 15.0-21.9) in patients with nonfatal cancer ($P = 0.012$).

Hematopoietic tumours (n = 21, 49%) were the most frequently reported type of malignancy (Figure 2). The median age at development of a hematopoietic tumour was 17.0 years (IQR 14.9-20.5), which was slightly lower compared to the other types of cancer (19.0 years, IQR 16.2-24.0, $P = 0.19$). The majority of hematopoietic tumours included Hodgkin and non-Hodgkin lymphomas (n = 7 and n = 8 respectively). Two patients with non-Hodgkin lymphomas were Epstein-Barr virus (EBV) positive (25%), 4 patients were EBV negative (50%) and the EBV status was unknown in 2 patients. None of the patients with Hodgkin lymphoma or non-Hodgkin lymphoma died. Three male patients (1 UC; 2 CD) were diagnosed with a hepatosplenic T-cell lymphoma (HSTCL, n = 3, 14.3%). All of the patients with HSTCL died. These 3 patients developed HSTCL at the age of 20.0, 18.0 and 23.0 years, after an IBD disease duration of 5.2, 6.0 and 5.3 years respectively. In all cases death occurred within a year after the HSTCL diagnosis at the age of 20.3, 19.0 and 23.5 years.

In patients diagnosed with colorectal carcinoma (CRC, n = 12, 29%), UC was the most frequent type of IBD (UC, n = 6; CD, n = 4; IBD-U, n = 2). The 4 CD patients who developed CRC all had disease confined to the colon (L2; Paris classification[18]). IBD disease duration to cancer in patients with CRC was significantly longer than in patients who developed a hematopoietic tumour, with a median duration of 9.3 years (IQR 4.3-11.8) vs 3.7 years (IQR 2.0-7.8, $P = 0.034$, Table S3). The youngest reported CRC patient was a female who developed CRC at the age of 14.5 years, 4 years after her initial IBD diagnosis. CRC was fatal in 25% of cases (n = 3), always within 1 year after cancer diagnosis. The youngest patient with a fatal outcome due to CRC was 19.5 years old when CRC was diagnosed, 9.0 years after her IBD disease diagnosis, and died after a period of 6 months.

Cholangiocarcinoma (CCA) was the third group of most frequently reported malignancies (n = 3, 7%, all male UC patients). Notably, all CCA cases were fatal and all patients had a concomitant diagnosis of primary sclerosing cholangitis (PSC). CCA was diagnosed after a median IBD duration of 12.9 years (IQR 5.0-16.0). The youngest reported CCA patient was 19 years old when his cancer was diagnosed and died within the same year, 14 years after his IBD diagnosis and 11 years after his PSC diagnosis. Of all patients who died due to an adenocarcinoma (CRC, n = 3, and CCA, n = 3), 67% (n = 4) had concomitant PSC.

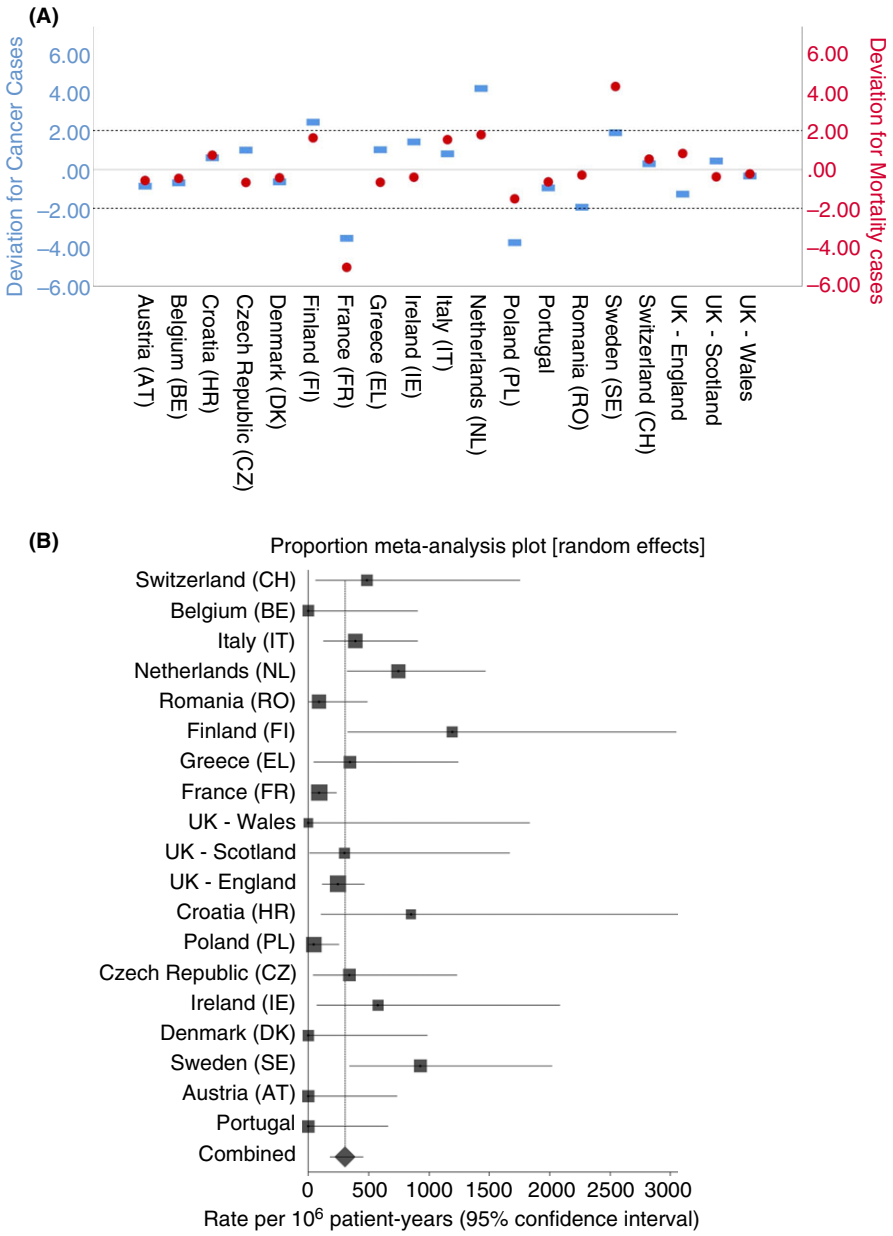

FIGURE 1 European incidence maps of malignancy and mortality in paediatric-onset IBD patients <26 years. A, The average incidence for all countries was used to calculate the expected number of cases per country according to their covered population. Deviation of the number of reported cancer and mortality cases from the expected number of cases is shown for European countries. B, Forest plot with 95% confidence intervals for each country. Random-effects model for meta-analysis was used due to high heterogeneity in the results to investigate the incidences of cancer and/or mortality

Other causes of cancer were melanoma (Clark's level 1) at the age of 12.4 years (n = 1), myeloid sarcoma (n = 1), neuroendocrine tumour with liver metastasis (n = 1), alveolar rhabdomyosarcoma (n = 1), thyroid carcinoma (n = 1), brain glioblastoma grade IV (n = 1) and renal cell carcinoma (n = 1).

3.4.1 | Malignancy and treatment: current exposure

Overall, virtually all patients who developed a hematopoietic malignancy (n = 21) had ever been exposed to thiopurines (n = 20, 95%, Table 4). With regard to the 3 months prior to their cancer diagnosis, the majority of these patients were exposed to thiopurine monotherapy (n = 12, 57%). Four patients with a hematopoietic malignancy used thiopurines in combination with a biologic (n = 4, 19%), while others were exposed to biologic monotherapy (n = 4, 19%) or were not using any medication (n = 1, 5%) in the 3 months prior to their cancer diagnosis (Figure 3).

Analysis of subgroups of hematopoietic tumours demonstrated that all patients who developed a HSTCL were exposed to thiopurines in the 3 months prior to their cancer diagnosis without concurrent or prior biologic exposure. We observed a numerically lower frequency of current exposure to thiopurine monotherapy in patients

TABLE 3 Patient characteristics of paediatric-onset IBD patients who developed a malignancy and/or had a fatal outcome

	Nonfatal cancer	Fatal cancer	Mortality due to other causes	Total	*P* value
Total patients, N	34	9	17	60	
Sex, N (%)					
Male	18 (52.9)	6 (66.7)	6 (35.3)	30 (50)	NS
Female	16 (47.1)	3 (33.3)	11 (64.7)	30 (50)	
IBD diagnosis, N (%)					
CD	20 (58.9)	4 (54.4)	9 (52.9)	33 (55.0)	
UC	11 (32.4)	5 (55.6)	5 (29.4)	21 (35.0)	
IBD-U	3 (8.7)	NA	3 (17.7)	6 (10.0)	
Age at IBD diagnosis					NS
Mean (SD)	12.3 (4.1)	12.1 (4.3)	10.3 (4.2)	11.7 (4.2)	
Median (IQR)	13.5 (10.6-15.4)	12.9 (8.3-15.4)	11.8 (7.7-13.5)	12.7 (9.0-14.8)	
Duration of disease to cancer, y					0.019[g]
Mean (SD)	5.5 (4.0)	9.1 (3.5)	NA	6.2 (4.1)	
Median (IQR)	4.3 (2.0-9.0)	9.1 (5.8-12.2)	NA	5.5 (2.8-9.5)	
Duration of disease to death, y					0.018[h]
Mean (SD)	NA	9.5 (3.4)	5.3 (4.8)	6.7 (4.8)	
Median (IQR)	NA	9.9 (6.4-13.0)	3.6 (1.6-8.0)	7.0 (2.1-10.0)	
Age at cancer, y					0.012[g]
Mean (SD)	17.7 (4.2)	21.0 (2.4)	NA	18.4 (4.1)	
Median (IQR)	16.6 (15.0-21.9)	20.0 (19.0-23.5)	NA	17.4 (16.0-22.0)	
Age at death, y					0.002[h]
Mean (SD)	NA	21.9 (2.8)	15.2 (5.4)	17.5 (5.7)	
Median (IQR)	NA	20.0 (19.5-24.7)	15.1 (12.9-18.8)	17.0 (14.0-21.8)	
Comorbidities					
PSC, N (%)	2 (5.9)	5 (55.6)	2 (11.8)	9 (15.0)	0.002[a]; NS[b]; NS[c]
Perianal disease, N (%)	9 (26.5)[d]	1 (11.1)[e]	6 (35.3)[e]	16 (26.7)[f]	NS

For comparison between 3 groups, the Fisher's exact test was used for categorical outcomes and the Kruskal-Wallis *H* test was used for continuous variables. If there was a statistically significant difference between the 3 groups, the Mann-Whitney test (continuous variables) or Fisher's exact test (categorical variables) was used to test differences between 2 groups.

NS, nonsignificant; NA, not applicable; PSC, primary sclerosing cholangitis; CD, Crohn's disease; UC, ulcerative colitis; IBD-U, IBD unclassified; IQR, interquartile range; SD, standard deviation; N, number; y, year.

[a]*P* value calculated with Fisher's exact test comparing nonfatal cancer vs fatal cancer.

[b]Nonfatal cancer vs mortality.

[c]Fatal cancer vs mortality.

[d]One missing value.

[e]Two missing values.

[f]Three missing values.

[g]*P* value calculated with Mann-Whitney test comparing nonfatal cancer vs fatal cancer.

[h]*P* value calculated with Mann-Whitney test comparing fatal cancer vs mortality.

diagnosed with an adenocarcinoma compared to patients with a hematopoietic tumour (n = 4, 27% vs n = 12, 57%, respectively, $P = 0.096$). Curiously, none of the 3 patients who developed a CCA were receiving a thiopurine or biologic.

3.4.2 | Malignancy and treatment: past exposure

There were no significant differences in percentage of patients with past exposure when comparing patients with hematopoietic cancer to patients who developed an adenocarcinoma (Table 4). Total duration of thiopurine exposure was numerically higher in the group of patients with an adenocarcinoma compared to patients who developed a hematopoietic tumour (median duration of 6.0 years [IQR 1.5-8.6] and 2.6 years [IQR 0.9-4.8] respectively; $P = 0.13$). This observation can be explained by the significantly longer IBD disease duration in patients diagnosed with an adenocarcinoma compared to patients with a hematopoietic tumour (9.5 years [IQR 5.0-12.0] vs 3.7 years [IQR 2.0-7.8], respectively, $P = 0.0064$).

All 3 patients with a HSTCL had been previously exposed to thiopurines. The median duration of thiopurine exposure in the 3 HSTCL patients was 4.2 years (IQR 4.0-5.0) compared with

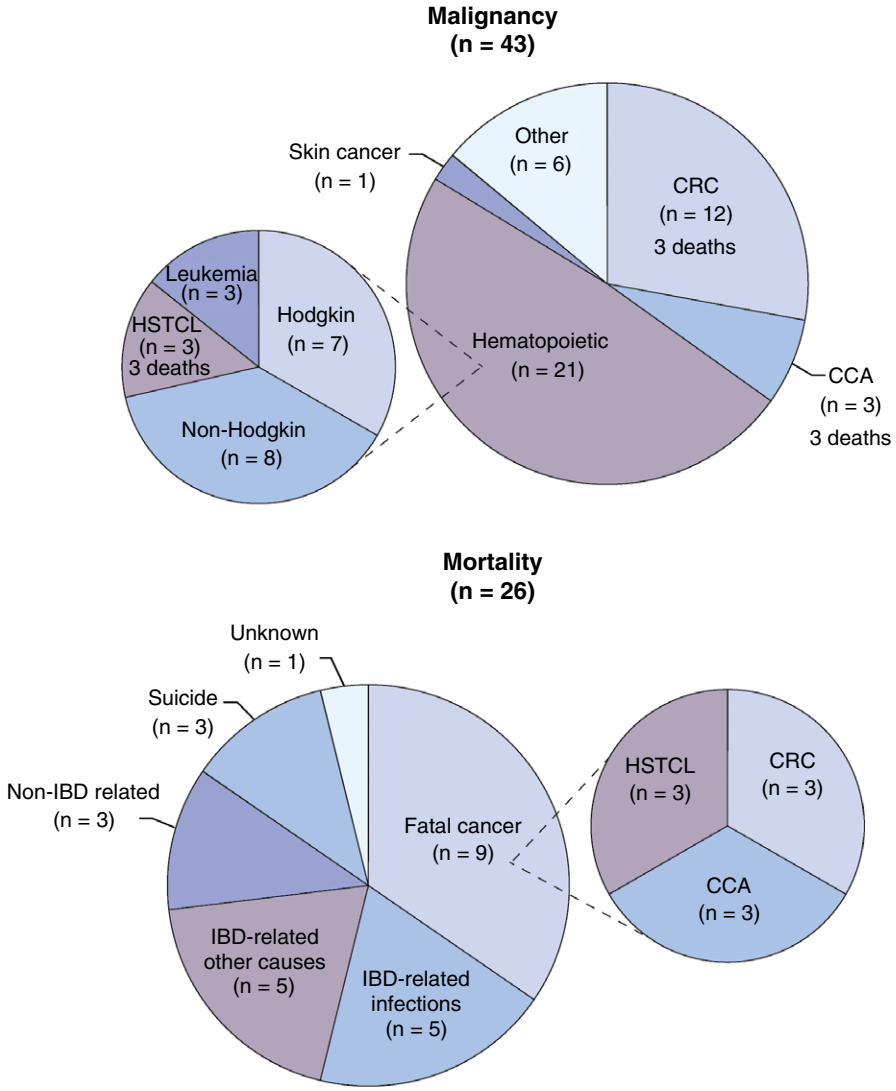

FIGURE 2 Causes of malignancy and mortality in paediatric-onset IBD patients (total cohort, n = 60). A total of 43 malignancies and 26 mortalities were included in our cohort. Patients who died due to cancer were diagnosed with CRC (n = 3), CCA (n = 3) and HSTCL (n = 3)

1.9 years (IQR 0.9-4.5) in the patients with other hematopoietic malignancies.

3.4.3 | Other risk factors

Fatal cancers consisted of CRC (n = 3), CCA (n = 3) and HSTCL (n = 3). In this total group of fatal cancers (n = 9), 56% of patients (n = 5) had a concomitant diagnosis of PSC, compared to 6% in the group of patients with nonfatal cancer (n = 2, $P = 0.002$; Table 3). The majority of patients with fatal cancer and a concomitant PSC diagnosis died due to adenocarcinomas (CCA, n = 3, CRC, n = 1, HSTCL, n = 1). CCA was diagnosed at a median duration of 4.9 years after the initial PSC diagnosis (IQR 0.04-8.9 years). The PSC patient who died of CRC was a male patient who developed IBD at the age of 14 years. He was diagnosed with both PSC and CRC at the age of 24 years.

Only a small number of patients who developed a malignancy had a positive family history for cancer (n = 5, 12%), consisting of 3 patients with a hematopoietic tumour (1 Hodgkin lymphoma, 1 non-Hodgkin lymphoma and 1 leukaemia) and 2 CRC patients. None of the patients who developed a malignancy had had a previous cancer diagnosis.

3.5 | Mortality

A total of 17 noncancer related deaths were reported during the study period (28%, Table 3). Patients who died due to noncancer-related causes were significantly younger than patients who died due to cancer (15.1 years [IQR 12.9-18.8] vs 20.0 years [IQR 19.0-23.5], $P = 0.002$, Table 3). Infections (29%, n = 5) were the main cause of noncancer-related deaths. These included 4 patients with sepsis and 1 patient who developed disseminated tuberculosis on anti-TNFα therapy (Figure 2 and Table 5). In addition to infectious causes, another 5 patients died due to IBD- or IBD therapy-related causes that were of non-infectious origin. Death due to liver failure occurred in a 16-year-old female with UC and PSC at 14.9 years of age. One patient died post-operatively, 2 days after a right hemi-colectomy for CD. One patient died of multi-organ failure complicating total

TABLE 4 Medication exposure in paediatric-onset IBD patients who developed a malignancy

	Total (n = 60)	**Hematopoietic (n = 21)**	HSTCL (n = 3)	Non-HSTCL (n = 18)	**Adenocarcinoma (n = 15)**	CRC (n = 12)	CCA (n = 3)	***P* value**
Current exposure								
Thiopurine monotherapy, N (%)	25 (41.7)	12 (57.1)	3 (100)	9 (50.0)	4 (26.7)	4 (33.3)	0 (0)	0.096
Biologic monotherapy, N (%)	11 (18.3)	4 (19.0)	0 (0)	4 (22.2)	2 (13.3)	2 (16.7)	0 (0)	1.00
Combination: Thiopurine + Biologic, N (%)	7 (11.7)	4 (19.0)	0 (0)	4 (22.2)	2 (13.3)	2 (16.7)	0 (0)	1.00
No medication, N (%)	9 (15.0)	1 (4.8)	0 (0)	1 (5.6)	3 (20.0)	1 (8.3)	2 (66.7)	0.287
Other medication, N (%)	8 (13.3)	0 (0.0)	0 (0)	0 (0)	4 (26.7)	3 (25.0)	1 (33.3)	0.023
Past exposure								
Thiopurine monotherapy, N (%)	25 (41.7)	9 (42.9)	3 (100)	6 (33.3)	5 (33.3)	4 (33.3)	1 (33.3)	0.732
Biologic monotherapy, N (%)	2 (3.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Combination: Thiopurine + Biologic, N (%)	17 (28.3)	8 (38.1)	0 (0)	8 (44.4)	4 (26.7)	4 (33.3)	0 (0)	0.721
No medication, N (%)	8 (13.3)	3 (14.3)	0 (0)	3 (16.7)	3 (20.0)	2 (16.7)	1 (33.3)	0.287
Other medication, N (%)	9 (15.0)	1 (4.8)	0 (0)	1 (5.6)	3 (20.0)	2 (16.7)	1 (33.3)	0.677
Total exposure								
Thiopurines (ever exposed, N (%)	49 (81.6)	20 (95.2)	3 (100)	17 (94.4)	10 (66.6)	9 (75.0)	1 (33.3)	0.063
Biologics (ever exposed), N (%)	22 (36.7)	9 (42.8)	0 (0)	9 (50.0)	5 (33.3)	5 (41.7)	0 (0)	0.732
Methotrexate (ever exposed), N (%)	9 (15.0)	3 (14.2)	0 (0)	3 (16.7)	2 (13.3)	2 (16.7)	0 (0)	1.00
Steroids (ever exposed), N (%)	44 (73.3)	16 (76.2)	3 (100)	13 (72.2)	11 (73.3)	9 (75.0)	2 (66.6)	1.00
Calcineurin inhibitor (ever exposed), N (%)	5 (8.3)	2 (9.5)	0 (0)	2 (11.1)	1 (6.7)	1 (8.3)	0 (0)	1.00
Duration of total exposure								
Duration thiopurine (y, median + IQR)	2.5 (0.9-5.7)[a]	2.6 (0.9-4.8)	4.2 (4.0-5.0)	1.9 (0.9-4.5)	6.0 (1.5-8.6)	6.0 (1.3-8.8)	6.0 (NA)	0.13
Duration biologic (y, median + IQR)	2.2 (0.6-4.0)[a]	3.0 (2.1-4.8)	NA	3.0 (2.1-4.8)	2.0 (0.3-2.5)	2.0 (0.3-2.5)	NA	0.083

P values are from Fisher's exact test for categorical variables. Definitions: Thiopurine monotherapy, exposure to thiopurines without any biologic exposure; Biological monotherapy, exposure to biologics without any thiopurine exposure; Combination therapy, combined exposure to thiopurines or biologics, either at the same time (n = 18 for the total group) or in consecutive fashion (only in 1 patient for the total group); Other medications, consisting of MTX, CAI and steroids; No medication, not using thiopurines, biologicals, MTX, CAI or steroids; Current exposure, exposure in the 3 mo prior to malignancy diagnosis or fatal outcome; Past exposure, exposure previous to the last 3 mo; Ever exposed, exposure at any time prior to the malignancy or fatal outcome.

CAI, calcineurin inhibitors, MTX, methotrexate, NA, not applicable; CD, Crohn's disease; UC, ulcerative colitis; IBD-U, IBD unclassified; IQR, interquartile range; SD, standard deviation; N, number; y, year.

[a]Two missing values.

parental nutrition. An additional 2 patients developed encephalopathy, but an infectious origin was not proven in either case.

Three patients committed apparent suicide. All 3 patients had severely complicated disease. One patient had PSC and failed liver transplantation. The second had severe perianal disease and enterocutaneous fistulas, and committed suicide after several years of in-patient care for repeated surgeries and severe postoperative complications. The third was a 15-year-old patient who underwent multiple procedures and had been surgically treated for perianal disease. Based on literature from national registries, the European incidence rate of suicide ranges between 10 and 40 per 1 000 000 in people aged 0-26 years.[19,20] Overall, the suicide incidence among paediatric-onset IBD patients was not found to be significantly different compared to the general population for this age group (RR = 0.45, 95% CI 0.14-1.45). Other causes of death were unrelated to disease or treatment (n = 3) or unknown (n = 1) and are shown in Table 5.

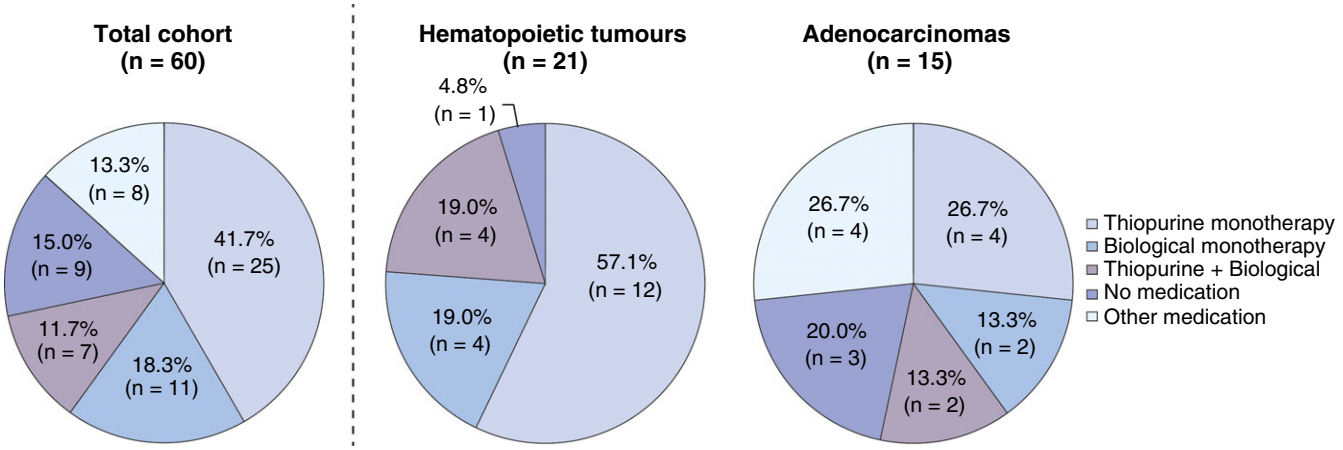

FIGURE 3 Medication exposure in paediatric-onset IBD patients in the 3 mo prior to malignancy or mortality diagnosis. Current exposure (in the 3 mo prior to severe outcome) was divided into (1) thiopurine monotherapy, (2) biologic monotherapy, (3) combination therapy of thiopurine with a biologic, (4) no medication or (5) other medication consisting of steroids, methotrexate, calcineurin inhibitors. Numbers and frequencies for the total cohort and patients who developed a hematopoietic malignancy or adenocarcinoma are shown

3.5.1 | Risk Factors and associated therapy for mortality

Four of the 5 (80%) patients who died due to an infectious cause were receiving immune suppression, of whom 2 were on dual immune-suppressive agents and the rest on a single drug (Table 5). Only 2 of those 4 patients were exposed to steroids at the moment of death. The remaining patient was not taking any medication. She had been previously exposed to combination therapy but refused all immunomodulatory or biological therapy 1 year before her death.

3.6 | Risks of malignancy and mortality in subpopulations

The RR of malignancy or mortality was not found to be significantly different between CD and UC patients from this cohort (RR = 0.99; 95% CI 0.40-2.46). When comparing patients with concomitant PSC to patients without PSC, a higher RR for fatal malignancy was found (RR = 7.08, 95% CI 2.34-21.44, $P = 0.0005$).

4 | DISCUSSION

In this first prospective multinational paediatric study to characterise malignancies and mortalities, we report the largest series of paediatric-onset IBD cases with these outcomes to date. Among the 26 identified fatalities over a 3-year period, 9 were due to malignancies, 10 were due to IBD or IBD-therapy related nonmalignant causes (including 5 infections), and suicide was the third leading cause. The most common identified risk factor for cancer-associated mortality was presence of PSC (50% of cases).

In our study, the cancer incidence among paediatric-onset IBD patients was not found to be significantly different compared to the general population for this age group. We used the higher estimates for pan-European paediatric-onset IBD prevalence in order to be conservative with estimates for malignancy and mortality. Despite our conservative approach, incidences among paediatric-onset IBD patients were higher compared to the general population in some countries, including Sweden, Finland and the Netherlands ($P = 0.007$, 0.011 and 0.007, respectively, Figure 1). As this study is unlikely to have bias from over-reporting, the data from these countries should raise some concern. When excluding countries with large negative deviation from the expected number of cases (ie Poland and France), the cancer incidence in paediatric-onset IBD patients aged 0-26 years increased to 230 per 1 000 000 (95% CI 157-326), demonstrating that these countries lowered the total reported incidence.

An increased RR for malignancy in paediatric-onset IBD patients has been established by several previous studies. Peneau et al identified 9 patients with cancer in 698 paediatric-onset IBD patients over a median follow-up period of 15 years, which translated into an increased risk of cancer in paediatric-onset IBD patients when compared to the background population (SIR 3.0 [95%CI 1.3–5.9]; $P < 0.02$).[8] More recently, data from a Swedish cohort also demonstrated a significantly increased adjusted hazard ratio for cancer in paediatric-onset IBD patients (2.2; 95% CI 2.0-2.5) compared to a matched general population over a 25-year follow-up period.[21,22] Gastrointestinal cancers had the highest RRs, with a hazard ratio of 134 (95% CI 59.6-382) for liver cancers and 19.5 (95% CI 14.7-26.2) for CRC.

The CCA and CRC were the most common type of neoplastic fatalities in our cohort (CCA, n = 3, CRC, n = 3). This is in line with the results reported in the EPIMAD study, where CRC was the only cause of neoplastic fatality among 698 paediatric-onset IBD patients followed over a course of 15 years.[8] In fact, in our cohort, HTSCL was only the third most common type of neoplastic fatality occurring in only 3 cases over 3 years. Fatal adenocarcinomas, which are highly likely to be associated with disease rather than treatment, were usually detected after >8 years of disease with the earliest occurrence at age 19. This suggests that current guidelines for surveillance in children and adults which recommend surveillance

TABLE 5 Medication exposure of paediatric-onset IBD patients who developed a fatal outcome

Cause of mortality	Total (n = 26)	Sex (M/F)	IBD type	Age at IBD diagnosis, y	Age at death, y	Current exposure			Previous exposure		
						Thiopurines	Biologics	Steroids	Thiopurines	Biologics	Steroids
Fatal cancer, N (%)	**9 (35)**										
CRC		F	CD	10.5	19.9	Yes	No	No	Yes	Yes	Yes
CRC		F	CD	6	20	Yes	No	Yes	Yes	No	No
CRC		F	UC	14.1	25.4	Yes	No	No	Yes	No	No
CCA		M	UC	12.9	26	No	No	Yes	No	No	Yes
CCA		M	UC	16	24	No	No	No	No	No	No
CCA		M	UC	5	19	No	No	Yes	Yes	No	No
HSTCL		M	CD	14.8	20	Yes	No	No	Yes	No	Yes
HSTCL		M	UC	12.0	19.0	Yes	No	No	Yes	No	Yes
HSTCL		M	CD	17.7	23.5	Yes	No	No	No	No	Yes
IBD-related deaths: infectious causes, N (%)	**5 (19)**										
Sepsis due to unknown infectious agent		F	CD	14	21	No	Yes	No	Yes	Yes	Yes
Sepsis due to unknown infectious agent		F	CD	13.3	22.6	No	No	No	Yes	Yes	No
Disseminated tuberculosis on IFX treatment		F	CD	11.8	12.8	No	Yes	Yes	Yes	Yes	Yes
Central line sepsis while on TPN		F	IBD-U	1.9	2.2	Yes	No	Yes	No	No	Yes
Joubert Syndrome with renal dysfunction and sepsis		F	UC	12.4	15.1	Yes	No	No	Yes	No	Yes
IBD-related deaths: other causes, N (%)	**5 (19)**										
Post-operatively		M	CD	13.5	15.4	Yes	No	No	Yes	No	No
Liver failure (in patient with concomitant PSC)		F	UC	14.9	16	No	No	Yes	Yes	No	Yes
Necrotising encephalitis		M	IBD-U	5	7.7	Yes	No	No	Yes	No	No
Acute necrotising encephalopathy		F	UC	13	13	No	No	Yes	No	No	Yes
Multi-organ failure while on TPN		F	CD	13.5	20.5	No	No	No	Yes	No	Yes
Suicide, N (%)	**3 (12)**										
Suicide		M	UC	2	12	No	No	Yes	No	No	Yes
Suicide		M	CD	7.9	25	No	No	No	Yes	Yes	Yes
Suicide		F	CD	9	15	No	Yes	Yes	No	Yes	Yes
Non-IBD-related deaths, N (%)	**3 (12)**										
Traffic accident		M	CD	9.1	17	No	Yes	No	Yes	Yes	Yes
Traffic accident		M	CD	11.6	13	No	Yes	No	No	Yes	Yes
Cardiac asthma caused by an aortic stenosis		F	IBD-U	7.6	15	Yes	No	No	Yes	No	Yes
Unknown, N (%)	**1 (4)**										
Unknown		F	UC	14.3	15.9	Yes	No	Yes	No	No	Yes

CD, Crohn's disease; UC, Ulcerative colitis; IBD-U, IBD unclassified; CRC, colorectal carcinoma; TPN, total parental nutrition; CCA, cholangiocarcinoma HSTCL, hepatosplenic T-cell lymphoma.

starting from 8 or 10 years of disease based on risk factors for CRC are adequate except in very rare cases.[23] Unfortunately, data on adherence to surveillance guidelines in our current cohort were not available. Paediatric and adult gastroenterologists treating patients with IBD should have increased awareness that these fatal malignant outcomes might occur in the second and third decades of life with early onset disease, and that patients with PSC should be followed closely including screening for CCA. It is interesting to note that all 3 patients with PSC-associated CCA were not receiving thiopurines or biologics. Thiopurines have been associated with a significant decrease in IBD-associated CRCs by van Schaik et al, while 5-ASA did not lead to a significant protective effect.[4] However, a recent French study found that 5-ASA was effective but questioned the efficacy of thiopurines.[24] Data regarding chemoprevention in IBD-associated PSC is a current research gap, highlighted by the increased risk for CRC and CCA in these patients at an early age.[24-26] In order to identify gaps and guide future research, details on all collected data for individual patients with PSC-related cancer and mortality in this cohort is provided in Table S4.

Despite a large number of patients, previous population-based studies on paediatric-onset IBD patients are underpowered with regard to drug exposure in patients who develop malignancy, and included patients that were older than in our series. A case series like this cannot truly determine causality between drug use and development of malignancy, but several observations from this study are important. Development of HSTCL is still a rare event, documented in only 3 patients over a 3-year period in the numerous countries surveyed. The 3 new cases identified by this prospective study occurred in patients that had been on current thiopurines without current or previous biologic exposure. This could suggest that current thiopurine exposure can be associated with these rare lymphomas in the absence of anti-TNF therapy. Similar to previous reports,[6,27-30] all patients were males. The recently published DEVELOP study did not evaluate the association between current exposure to drugs and cancer[7], although current exposure and not previous exposure to thiopurines seems to be more important for development of lymphomas.[9] However, the DEVELOP study did demonstrate that exposure to combination therapy, but not to thiopurines or infliximab monotherapy, was associated with an increase in risk for malignancy, with an adjusted SIR of 3.06 for developing a cancer if combination therapy of a biologic and a thiopurine was used. Another interesting observation in our study is that the majority of patients who developed a hematopoietic malignancy had been exposed to thiopurines (n = 20, 95%). In fact 71% (n = 15) were exposed to thiopurines in the last 3 months prior to their diagnosis; which is significantly higher compared to patients who developed adenocarcinomas ($P = 0.041$). Altogether this suggests that current exposure and not previous exposure to thiopurines seems to be more important for development of lymphomas in paediatric-onset IBD patients, which is in line with the findings in adult patients by the CESAME study group.

The second leading cause of fatalities in young patients with IBD was likely associated with therapy. Five patients died from presumed or proven infections, and 4 of 5 were receiving concomitant immune suppression. Two patients died from necrotising encephalopathy of unknown origin, which could have been infectious. In a previous retrospective study by the Porto group, combination therapy with any combination of 2 immune suppressive drugs was associated with infection-associated mortality.[6] In that study, 86% of patients developing a fatal infection or sepsis had received 2 or more immune-suppressive agents. The current study identified fewer cases of infectious mortality than the previous study but covered a shorter period of time (3 vs 5 years).

Surprisingly, suicides were the third most common reason for fatalities, surpassing procedural complications (n = 2), thromboembolic events (n = 0) and liver disease (n = 1). It is important to be cautious when interpreting suicides because data regarding previous mental health and other comorbidities are not available. The 3 cases reported all involved patients with a severe complicated course, including patients with repeated liver and stem cell transplantations for refractory disease. In fact, 1 suicide occurred during a hospital admission. Although suicide incidence was not significantly increased compared to the general population, the suicide cases may be indirectly considered disease-related deaths. This emphasises the importance of psychological support in addition to medical treatment in paediatric-onset IBD patients.

Our study provides important insight regarding severe outcomes of paediatric-onset IBD but is not without limitations. First, our results suggest under-reporting in several countries. To avoid underestimation of incidence rates in a multinational setup, it is pivotal to obtain registry-based denominator data in future studies. In addition, lower response rates among adult gastroenterologists and differences in practice between the participating countries may have contributed to under-reporting of malignancies after transition to adult care and may have added bias to the reported data. Secondly, the use of thiopurines has become increasingly contentious, since the link between thiopurines and lymphomas[9,31] and skin cancers[32] has become available. It would be very easy to over-interpret data and assign risk to therapy in the cases with hematopoietic malignancies. However, a case series cannot adjust for underlying age-adjusted population risk. With the exception of HSTCL, hematopoietic malignancies do occur in healthy adolescents without underlying disease or exposure to drugs. Since paediatric-onset IBD tends to be aggressive and extensive, thiopurines are used very early in the disease in a large proportion of patients. Thus, clear associations between therapy and malignancies will require analysis adjusted for underlying risk of IBD and cancer in populations being explored. Current studies that have limited analysis to past exposure are insufficient. We therefore need long-term, prospective data on all children and adults via fully consented (international) registers to provide perspective regarding risk from disease and from therapy.

In conclusion, data from this multinational cohort with the largest number of paediatric-onset IBD patients with cancer and/or fatal outcome to date, suggest that fatal outcomes and malignancies are still rare events. However, PSC appears to be a significant risk factor. While current guidelines for surveillance in children appear to be

adequate, our data raise the question whether chemoprevention in IBD patients with concomitant PSC should be instituted. Future analysis of databases in participating countries may allow us to better evaluate the RRs for paediatric-onset IBD patients compared to the background population.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section at the end of the article.

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APPENDIX 1

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