Childhood onset inflammatory bowel disease and risk of cancer: a Swedish nationwide cohort study 1964-2014

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ABSTRACT

OBJECTIVE
To assess risk of cancer in patients with childhood onset inflammatory bowel disease in childhood and adulthood.

DESIGN
Cohort study with matched general population reference individuals using multivariable Cox regression to estimate hazard ratios.

SETTING
Swedish national patient register (both inpatient and non-primary outpatient care) 1964-2014.

PARTICIPANTS
Incident cases of childhood onset (<18 years) inflammatory bowel disease (n=9405; ulcerative colitis, n=4648; Crohn’s disease, n=3768; unclassified, n=989) compared with 92 870 comparators from the general population matched for sex, age, birth year, and county.

MAIN OUTCOME MEASURES
Any cancer and cancer types according to the Swedish Cancer Register.

RESULTS
During follow-up through adulthood (median age at end of follow-up 27 years), 497 (3.3 per 1000 person years) people with childhood onset inflammatory bowel disease had first cancers, compared with 2256 (1.5 per 1000 person years) in the general population comparators (hazard ratio 2.2, 95% confidence interval 2.0 to 2.5). Hazard ratios for any cancer were 2.6 in ulcerative colitis (2.3 to 3.0) and 1.7 in Crohn’s disease (1.5 to 2.1). Patients also had an increased risk of cancer before their 18th birthday (2.7, 1.6 to 4.4; 20 cancers in 9405 patients, 0.6 per1000 person years). Gastrointestinal cancers had the highest relative risks, with a hazard ratio of 18.0 (14.4 to 22.7) corresponding to 202 cancers in patients with inflammatory bowel disease. The increased risk of cancer (before 25th birthday) was similar over time (1964-1989: 1.6, 1.0 to 2.4; 1990-2001: 2.3, 1.5 to 3.3); 2002-06: 2.9, 1.9 to 4.2; 2007-14: 2.2, 1.1 to 4.2).

CONCLUSION
Childhood onset inflammatory bowel disease is associated with an increased risk of any cancer, especially gastrointestinal cancers, both in childhood and later in life. The higher risk of cancer has not fallen over time.

Introduction
Ulcerative colitis and Crohn’s disease have been linked to colorectal cancer.1 2 Based primarily on studies of adult onset inflammatory bowel disease, the risk seems to be particularly high in those with longstanding extensive colitis (both ulcerative colitis and Crohn’s disease).3 Additional risk factors include a family history of colorectal cancer4 and concomitant primary sclerosing cholangitis.5 6

The childhood onset inflammatory bowel disease phenotype is characterised by many of the same traits as adult onset disease associated with cancer, including more extensive disease spread,7 8 a more severe phenotype,9 10 increased use of immunomodulatory treatment,11 and longer duration (for follow-up through adulthood). Investigations of childhood onset inflammatory bowel disease and risk of cancer during childhood and adulthood are rare and lack details of absolute and relative risks. Specifically, risk assessments for different ages of onset, phenotypes, calendar trends, and different cancer types are lacking (table 1).12 17

The lack of data for childhood onset inflammatory bowel disease is especially worrisome given the increasing incidence and prevalence of paediatric Crohn’s disease (mainly colitis).18 19 Moreover, cancer risk in inflammatory bowel disease might have changed owing to changes in management since the introduction of biological agents and a corresponding tendency to avoid surgery or perform it later.20 Recent data have shown a decreasing incidence of colorectal cancer in patients with inflammatory bowel disease,21 but those studies have primarily focused on adult onset disease. The European Crohn’s and Colitis Organisation recommends that patients with adult onset ulcerative colitis undergo surveillance colonoscopies every 6-8 years after disease onset.22 But no evidence based guidelines exist for surveillance of colorectal cancer in childhood onset inflammatory bowel disease.23 24 Guidelines for childhood onset Crohn’s disease do not mention surveillance for colorectal cancer23 and refer to adult guidelines regarding ulcerative colitis.25

Although colorectal cancer has been studied more than any other cancer in adult inflammatory bowel disease, there is limited data for childhood onset disease. Few studies have explored the association between childhood onset inflammatory bowel disease and malignancy. Most previous studies have limited power, are not widely applicable, or lack phenotype information and have not explored potential changes in cancer risk over time.

WHAT IS ALREADY KNOWN ON THIS TOPIC
Few studies have explored the association between childhood onset inflammatory bowel disease and malignancy. Most previous studies have limited power, are not widely applicable, or lack phenotype information and have not explored potential changes in cancer risk over time.

WHAT THIS STUDY ADDS
Our data show that patients with childhood onset inflammatory bowel disease have an increased risk of cancer, especially gastrointestinal cancers, lymphoid neoplasms, and skin cancer, both in childhood and later in life. The relative risk of cancer does not seem to have diminished over time.
bowel disease, other cancers might be more relevant during childhood and adolescence. In a recent European survey of 18 cancer cases in children with inflammatory bowel disease, several patients had haematopoietic cancers, but no patient had colorectal cancer. In a US study of 1374 children followed for 6624 patient years, only two children developed colorectal cancer (lymphoma), and a Danish study that included patients with inflammatory bowel disease (onset before 20 years) found that those with Crohn’s disease or ulcerative colitis were not at increased risk of haematological cancers. Adult inflammatory bowel disease has been linked to an increased risk of haematopoietic cancers, but no patient had colorectal cancer. In a recent European survey of 18 cancer cases in children with inflammatory bowel disease, several patients had haematopoietic cancers, but no patient had colorectal cancer. In a US study of 1374 children followed for 6624 patient years, only two children developed colorectal cancer (lymphoma), and a Danish study that included patients with inflammatory bowel disease (onset before 20 years) found that those with Crohn’s disease or ulcerative colitis were not at increased risk of haematological cancers.26 Adult inflammatory bowel disease has been linked to an increased risk of malignant melanoma and non-melanoma skin cancer,27 but whether such risk applies to childhood onset disease is unclear.

We linked nationwide data on childhood onset inflammatory bowel disease with data on cancer from the Swedish Cancer Register to provide data on relative and absolute risks of cancer. We analysed the risks of cancer overall, for subtypes, and across calendar periods.

Methods

Study design

In a nationwide, register based cohort study, we compared the incidence of cancer in patients with childhood onset (<18 years) inflammatory bowel disease with general population reference individuals matched for sex, age, date of birth (± twelve months), and place of residence.

Setting

In Sweden, patients with inflammatory bowel disease are treated by paediatric gastroenterologists in childhood and by gastroenterologists in adulthood. All residents have access to publicly funded healthcare including inpatient care. Using the unique personal identity number issued to all Swedish residents,30 we linked data from administrative and clinical national registers on demographics,31 drugs,32 morbidity,33 34 and mortality.35 These virtually complete registers enable prospective assessment independent of residence, socioeconomic status, and disease severity.

Study population

We identified all people in Sweden with a first diagnosis of inflammatory bowel disease with data on cancer from the Swedish Cancer Register to provide data on relative and absolute risks of cancer. We analysed the risks of cancer overall, for subtypes, and across calendar periods.

In previous sensitivity analyses we and others have found the best definition of onset in both children and adults to be two or more diagnostic listings of inflammatory bowel disease.36-38 In a recent validation study, we found that 93% of patients with two or more diagnostic listings in the registers39 were confirmed to have inflammatory bowel disease when their medical

Table 1 | Childhood onset inflammatory bowel disease and risk of cancer

| Study       | Study period | Age at onset, years | No of patients followed (sub-type) | Patient years of follow-up | Number of cancers diagnosed | Incidence per 1000 person years (95% CI) | Relative risk* |
|-------------|--------------|---------------------|-----------------------------------|---------------------------|----------------------------|----------------------------------------|----------------|
| Devroede, 1971 | USA 1919-65  | <14                 | 396 (UC)                          | NR, max 43 years          | 52 (any cancer)            | 1.0 (0.5 to 2.1) for CRC                | NA             |
| Weedon, 1973  | USA 1919-65  | <22 (mean 15)       | 449 (CD)                          | 7077                      | 12 (any cancer) 8 (CRC)    | 3.3 (0.2 to 16.3) NR                   | NA             |
| Goel, 1973    | Scotland 1931-71 | <14 (mean 8)       | 25 (UC)                           | 303                       | 1 (CRC)                   | 3.1 (1.7 to 16.3) 118 (63 to 202)       | NA             |
| Ekbom, 1990  | Sweden 1945-83 | <15                 | 363 (UC)                          | 4220                      | 13 (CRC)                  | 0.4 (0.2 to 0.9) 10 (3 to 23)           | NA             |
| Ashworth, 2013 | France 1988-2009 | <17 (median 14)   | 698 (UC,CD)                       | NR, median 12 years       | 9 (any cancer)            | 3.0 (1.3 to 5.9) NA                    | NA             |
| Jess, 2012    | Denmark 1979-2008 | <20               | 4763 (UC,CD)                      | 52 100                    | 18 (CRC)                  | 3.3 (3.1 to 3.6)§ UC: 2.0 (1.4 to 2.7) CD: 2.3 (1.5 to 3.4) | NA             |
| Peneau, 2013  | France 1988-2009 | <17 (median 14)   | 698 (UC,CD)                       | NR, median 12 years       | 9 (any cancer)            | 3.0 (1.3 to 5.9) NA                    | NA             |
| de Ridder, 2014 | Denmark 1978-2010 | <19 (median 12) | NA                                | NA                        | 18 (any cancer) NA NA NA NA | NA             |
| Kappelman, 2014 | Denmark 1978-2010 | <20               | NR (UC,CD)                        | NR                        | NR                        | NR                      | NA             |
| Hyams, 2017   | USA, Europe 2007-16 | <17               | 5766 (UC,CD)                      | 24 543                    | 15 (any cancer) 9 (lymphoid) | 0.6 (0.4 to 1.0)§ Thio exposed: 2.9 (1.4 to 5.1) Non-exposed: 1.3 (0.2 to 4.7) | NA             |
| Current study | Sweden 1964-2014 | <18 (median 15)   | 9405 (UC,CD)                      | 148 682                   | 497 (any cancer) 122 (CRC) 24 (lymphoid) | 3.3 (3.1 to 3.6)$ HR for any cancer: UC: 2.6 (2.3 to 3.0) CD: 1.7 (1.5 to 2.1) HR for CRC UC: 32 (23 to 49) CD: 5.8 (3.2 to 10) | NA             |

CD=Crohn’s disease; CI=confidence interval; CRC=colorectal cancer; HR=Hazard Ratio; NA=Not applicable; NR=not reported; thi=thiopurines; UC=ulcerative colitis.

*Standardised incidence ratio, unless otherwise stated
†Followed up until 3rd birthday
‡Followed up until 18th birthday
§Followed up until 23rd birthday

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records were reviewed. To increase the specificity of the exposure we restricted our population to patients with at least two visits or admissions to hospital listing a diagnosis of inflammatory bowel disease (supplementary figure S1). Ulcerative colitis, Crohn’s disease, and inflammatory bowel disease unclassified were defined at the start of follow-up using the first two diagnostic codes only (supplementary table S1). All analyses of cancer incidence in patients with ulcerative colitis, Crohn’s disease, and inflammatory bowel disease unclassified were based on this definition.

At the end of follow-up, we used different definitions for ulcerative colitis, Crohn’s disease, and inflammatory bowel disease unclassified in the descriptive statistics of the study population. Different inflammatory bowel disease diagnoses might be documented in a patient’s medical history, either owing to a colitis that is hard to distinguish between ulcerative colitis and Crohn’s disease or because of incorrect registration in the records. We therefore classified patients with a mixture of codes for ulcerative colitis, Crohn’s disease, or indeterminate colitis (ICD-10 code K52.3) during follow-up as inflammatory bowel disease unclassified. Moreover, patients who had codes for both ulcerative colitis and Crohn’s disease and were diagnosed as having only ulcerative colitis or Crohn’s disease in the past five years were classified as ulcerative colitis or Crohn’s disease, respectively. Finally, patients who had a diagnostic or procedure code typical of Crohn’s disease (such as small bowel resection or Crohn’s disease of the small bowel, supplementary table S2a) were classified as having Crohn’s disease. The directions of these reclassifications are summarised in supplementary table S2b.

For each patient with inflammatory bowel disease we randomly selected up to 10 reference individuals from the Swedish Population Register31 (which includes all Swedish residents) matched for sex, year of birth, and place of residence (n=92,870). Each population based reference individual had to be alive and living in Sweden at the date of the second visit for inflammatory bowel disease of their corresponding patient to avoid immortal time bias and was assigned the date of their first diagnosis as start of the follow-up. Reference individuals had to be free of inflammatory bowel disease at the index date of their respective case but could be diagnosed with inflammatory bowel disease at a later date (and would then stop contributing risk time to the reference population). They could theoretically be sampled as a reference individual to multiple cases.

**Phenotypes of inflammatory bowel disease**

Age of onset and phenotype of inflammatory bowel disease (extent of ulcerative colitis and localisation and behaviour of Crohn’s disease) at the end of follow-up was defined using the Paris classification39 from the start of ICD-10 in 1997. Codes used are summarised in supplementary table S3.

Extra-intestinal manifestations in the skin, eyes, or joints and primary sclerosing cholangitis at any time during follow-up were defined using the relevant ICD codes (supplementary table S4).

**Surgery**

Surgery related to inflammatory bowel disease included colectomies, other bowel surgery, and perianal surgery. We identified dates of surgery from inpatient care (after 1 January 1964) and from outpatient specialist care (after 1 January 1997). We used the NOMESCO classification of surgical procedures (supplementary table S5).

**Drugs**

The Swedish Prescribed Drug Register started on 1 July 2005 and contains data on the dispensation of all prescribed drugs but not drugs dispensed in a hospital or bought over the counter. The anatomical therapeutic chemical codes used in descriptive statistics are listed in supplementary table S6. Information about total enteral nutrition is not available in these national registers. Adalimumab, an inhibitor of tumour necrosis factor (TNF), has 100% coverage in the Prescribed Drug Register.32 Another TNF inhibitor, infliximab, is given as an infusion in hospital and is typically not found in the register (about 20% of all sold infliximab doses are found in the register). In Stockholm County (20% of the population of Sweden) close to all infliximab infusions are found in the patient register (2007-14),42 so the total coverage of infliximab treatment in the national registers is approximately 30-40% (about 70% of all dispensed doses of TNF inhibitors (infliximab plus adalimumab) were captured in the registers).

**Cancer**

The National Swedish Cancer Register, established in 1958, records all newly diagnosed malignant tumours in Sweden (supplementary table S7). All healthcare providers in Sweden must report new cancer diagnoses to the register, which has an estimated completeness of >96%.34

**First degree relatives**

The Swedish Multigeneration Register includes people born since 1932 and those who are registered as residents in Sweden after 1961. The register contains information on people and their biological parents, enabling links between parents, children, and their siblings.42 We used the Swedish Multigeneration Register to identify all first degree relatives to children with inflammatory bowel disease and their matched reference individuals. Through linkage of first degree relatives to the patient and cancer registers, we assessed the occurrence of cancer and inflammatory bowel disease in the family to study potential effect modification of family history.

**Statistics**

Patients were considered at risk of their first cancer from their first visit with a diagnosis of inflammatory bowel disease (or the corresponding index date for reference individuals) until the occurrence of first
cancer or censoring owing to death, emigration, end of follow-up, or change of inflammatory bowel disease status (that is, reference individuals later diagnosed with inflammatory bowel disease), whichever came first. We analysed the risk of cancer before the 18th birthday, 25th birthday, and throughout follow-up. Because the phenotype, incidence, and medical care of inflammatory bowel disease have changed over time, we analysed the risk of cancer over different time periods. From 1964 to 2000, incident cases of inflammatory bowel disease were identified only in inpatient care. Patients identified as new cases of inflammatory bowel disease in 2001 (when the register started including outpatient care) are therefore a mixture of truly incident cases and people who had never been inpatients but were identified for the first time in the outpatient setting (supplement 12). Consequently, we analysed the years 1964-2001 and 2002-14 separately. In all main analyses, the type of inflammatory bowel disease (ulcerative colitis, Crohn’s disease, or inflammatory bowel disease unclassified) was determined by the first two diagnostic listings only (because the definition of exposure is not supposed to “look into the future”). In sensitivity analyses, the type of inflammatory bowel disease was determined using all available information at the end of follow-up. Finally, when analysing stratum specific hazard ratios for different exposures that occurred during follow-up (such as extra-intestinal manifestations, primary sclerosing cholangitis, colitis, bowel or perianal surgery, and drugs) exposure was considered to start from the date of the corresponding register entry; follow-up of “colitis ≥10 years before start of follow-up” started 10 years after the first diagnostic listing of colitis.

Anyone who had cancer before the index date was excluded. When estimating the risk of colon or rectal cancer, patients were additionally censored at the date of total colectomy or rectum amputation (supplementary table S5). For patients diagnosed with colorectal cancer in the first three months after colectomy, date of cancer was considered to be the date of colectomy. In a sensitivity analysis, we compared the cumulative incidence of colorectal cancer between patients with childhood onset inflammatory bowel disease and patients with other ages of onset.

We calculated crude rates by dividing the number of cancers (all and subtypes) diagnosed during follow-up by the corresponding person time at risk. To compare the risk of cancer between childhood onset inflammatory bowel disease cases and non-inflammatory bowel disease reference individuals we computed hazard ratios and 95% confidence intervals using Cox proportional hazards models adjusted for sex, age, birth year, and place of residence. The proportional hazards assumption was checked by testing the Schoenfeld residuals followed by visual inspection of the complementary log-log survival curves. We saw no marked departures from the assumption.

We also explored the possibility that the effect of inflammatory bowel disease on the risk of cancer was modified by heredity by evaluating the interaction term between inflammatory bowel disease and having a first degree relative with cancer before age 50. In sensitivity analyses we excluded study participants diagnosed as having cancer in the first year of follow-up. To avoid confounding because of differences in attained age across calendar periods, we performed all comparisons between calendar periods restricted to cancers diagnosed before 18th or 25th birthdays. In a sensitivity analysis, we also compared the cumulative incidence of colorectal cancer between patients with different ages of onset of inflammatory bowel disease (log-rank test).

Statistical analyses were performed using R statistical software (version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria) and the survival package (version 2.38, Therneau, T (2015), https://CRAN.R-project.org/package=survival). A P value less than 0.05 was considered statistically significant; confidence intervals were computed by inversion of the likelihood ratio test statistics.

This study was approved by the Ethics Review Board in Stockholm (2007/785-31/5; 2011/1509-32; 2015/0004-31). Because this study was strictly register based, individual informed consent was not deemed necessary.43

Patient involvement
No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. We plan to disseminate the results of the research to the relevant patient community.

Results

Background data
We identified 9405 patients with childhood onset inflammatory bowel disease for the period 1964-2014 (ulcerative colitis n=4648, 49%; Crohn’s disease: n=3768, 41%; inflammatory bowel disease unclassified: n=989, 11%) (supplementary figure S1, table 2).

The male:female ratio was close to one, the median age of first diagnosis of inflammatory bowel disease was 15 years, and the median age at end of follow-up was 27 years (fig 1, table 3). Approximately half of patients had their first visit listing a diagnosis of inflammatory bowel disease in 2002 or later (n=4642). The distribution of age at first diagnosis did not differ between 1964 and 2001 or between 2002 and 2014, although naturally it did differ at the end of follow-up. Most patients with ulcerative colitis had total colitis and most patients with Crohn’s disease had colonic involvement. More than one fifth of all patients with inflammatory bowel disease had colitis with duration of ≥10 years (table 3).
Main results
In 148 682 person years of follow-up, we found 497 first cancers in patients with childhood onset inflammatory bowel disease (3.3 per 1000 person years), compared with 2256 cancers in matched reference individuals in 1 486 983 person years (1.5 per 1000 person years). This corresponds to one extra case of cancer for every 556 patients with inflammatory bowel disease followed for a year, compared with reference individuals (1/risk difference) (table 4).

People with childhood onset inflammatory bowel disease were at a more than twofold risk of cancer (2.2, 2.0 to 2.5). Relative risk was higher in ulcerative colitis (2.6, 2.3 to 3.0) than in Crohn’s disease (1.7, 1.5 to 2.1) (P<0.001, supplementary table S9a). Relative risks were increased in the first year after diagnosis (based on eight cancers: five lymphoid neoplasms, two colorectal cancers, and one small bowel cancer) and remained statistically significantly higher at five years of follow-up and onwards (fig 2, supplementary tables S9a-d).

Incidence rates for cancer were higher in girls than boys (4.0 per 1000 v 2.8 per 1000 person years, supplementary tables S8a-c), but because background rates for cancer also differed, this translated into a higher hazard ratio for cancer in boys (4.6, 4.4 to 5.4, compared with 1.5, 1.4 to 1.7, in girls) (P<0.001, fig 2, supplementary tables S9a-d). The hazard ratio for cancer in inflammatory bowel disease was higher with younger age (linear term) at first diagnosis (P=0.006, fig 2, supplementary tables S9a-d), and absolute incidence rates increased with age (fig 3). Note that the sudden rise in cancer after 45 years of follow-up is based on a very small number of people.

We performed all retrospective analyses stratified by ulcerative colitis and Crohn’s disease using the definitions at the end of follow-up (table 2, supplementary table S2b). This did not change results more than marginally (data not shown).

Inflammatory bowel disease phenotypes, drugs, and heredity
Using ICD codes as proxies, we analysed the risk of cancer as a function of phenotype (all absolute incidence rates, in total and for different phenotypes) (fig 2, supplementary tables S9a-d). Most relative risk estimates for cancer were similar after restricting our data to cases with the first diagnosis of inflammatory bowel disease after the introduction of biological agents—diagnosed in 2002-14 (supplementary tables S9c-d).

Risk of cancer was much higher in patients with a diagnosis of primary sclerosing cholangitis (6.6, 4.9 to 8.7) and in patients with longstanding (>10 years) colitis (3.9, 2.9 to 5.0) (fig 2, supplementary table S9a). Patients with extra-intestinal manifestations or who had undergone surgery (bowel surgery or perianal surgery) did not have an increased risk of cancer compared with the overall inflammatory bowel disease population (fig 2, supplementary table S9a). Among
2114 children who were ever treated with thiopurines during follow-up since 1 July 2005, we identified 15 cases of any cancer, two of which developed in patients who also received a TNF inhibitor at some point. Confidence intervals were wide and overlapping with no significant differences between groups of different drug exposures (overall $P=0.3$, supplementary tables S8a-c and S9a-c). Having a first degree relative with any cancer before 50 years of age was associated with a higher risk of cancer in patients with ulcerative colitis (4.4, 3.2 to 5.8; $P_{\text{interaction}}=0.03$), but this effect was not significant in Crohn’s disease or inflammatory bowel disease overall ($P_{\text{interaction}}=0.26$ and 0.06, respectively) (supplementary table S9a).

**Type of cancer**

We found an increased risk of several cancers in inflammatory bowel disease (fig 4) and supplementary Table 3 | Characteristics at end of follow-up in patients with childhood onset (<18 years) inflammatory bowel disease, diagnosed in Sweden since 1964 and followed up through 2014. Numbers are n (%), unless otherwise stated.

| Characteristic                                           | Inflammatory bowel disease | Ulcerative Colitis | Crohn’s disease | IBD unclassified |
|----------------------------------------------------------|----------------------------|-------------------|-----------------|------------------|
| Total                                                    | 9405                       | 3991 (42.4)       | 4272 (45.4)     | 1142 (12.1)      |
| Age at end of follow-up (years):                         |                            |                   |                 |                  |
| Mean (SD)                                                | 30 (12)                    | 30 (12)           | 30 (13)         | 23 (10)          |
| Median (IQR)                                             | 27 (21-37)                 | 28 (22-38)        | 27 (21-40)      | 22 (18-27)       |
| 0 to <30                                                 | 5756 (61.2)                | 2305 (57.8)       | 2507 (58.7)     | 964 (82.7)       |
| ≥30 to <45                                               | 2379 (24.8)                | 1140 (28.6)       | 1043 (24.4)     | 446 (38.8)       |
| ≥45                                                      | 1320 (14.0)                | 546 (13.7)        | 722 (16.9)      | 52 (4.6)         |

Reason for end of follow-up:

- Malignancy: 497 (5.3) 266 (6.7) 200 (4.7) 31 (2.7)
- Death: 305 (3.2) 174 (4.4) 116 (2.7) 15 (1.3)
- Emigration: 145 (1.5) 68 (1.7) 64 (1.5) 13 (1.1)

31 December 2014: 8615 (91.6) 3581 (89.7) 3943 (92.3) 1091 (95.5)

Length of follow-up (years):

- To <1: 323 (3.4) 115 (2.9) 147 (3.4) 61 (5.3)
- ≥1 to <5: 1391 (14.8) 469 (11.8) 582 (13.6) 340 (29.8)
- ≥5 to <10: 2010 (21.4) 787 (19.7) 900 (21.1) 323 (28.3)
- ≥10 to <20: 2785 (29.6) 1277 (32.0) 1227 (28.7) 381 (26.4)
- ≥20: 2896 (30.8) 1343 (33.7) 1416 (33.1) 137 (12.0)

Maximum Paris endoscopy classification during follow-up:

| Classification                                                                 | Ulcerative Colitis | Crohn’s disease | IBD unclassified |
|-------------------------------------------------------------------------------|--------------------|-----------------|------------------|
| NA                                                                            | 3651 (100)         | 4048 (100)      | 1106 (100)       |
| E1 (proctitis)                                                                | 179 (4.9)          | NA              | 45 (4.1)         |
| E2 (left sided colitis)                                                       | 315 (8.6)          | NA              | 77 (7.0)         |
| E3E4 (total/pan colitis)                                                      | 2402 (65.8)        | NA              | 504 (46.6)       |
| L1 (terminal ileitis)                                                         | 755 (20.7)         | 80 (6.4)        | 480 (43.4)       |
| L2 (colon)                                                                    | NA                 | 1103 (27.2)     | NA               |
| L3LX (ileoceleal or not defined)                                              | NA                 | 1303 (34.2)     | NA               |
| B1 (non strictureing/penetrating)                                             | NA                 | 1113 (27.5)     | NA               |
| B2 (strictureing)                                                             | NA                 | 3198 (79.0)     | NA               |
| B3 (penetrating)                                                              | NA                 | 373 (9.2)       | NA               |
| B2B3 (strictureing and penetrating)                                           | NA                 | 338 (8.3)       | NA               |
| P (penial disease modifier)                                                   | NA                 | 139 (3.4)       | NA               |

Complications during follow-up:

- Extra intestinal manifestations: 592 (6.3) 185 (4.6) 333 (7.8) 74 (6.5)
- Primary sclerosing cholangitis: 705 (7.5) 451 (11.3) 124 (2.9) 130 (11.4)
- Colitis during follow-up:
  - Colitis ≥10 years: 2233 (23.7) 1098 (27.5) 920 (21.5) 215 (18.8)
  - Colitis ever: 5359 (57.0) 2421 (60.7) 1979 (46.3) 959 (84.0)
- Surgery:
  - Bowel surgery: 2522 (26.8) 725 (18.2) 1697 (39.7) 100 (8.8)
  - Perianal surgery: 1134 (12.1) 204 (5.1) 930 (21.8) 0 (0.0)
- Drugs:
  - Incident cases from 1 July 2005*: 3383 1231 1459 693
  - Neither thiopurines nor TNF inhibitors: 1257 (37.2) 607 (49.3) 387 (26.5) 263 (38.0)
  - Only thiopurines: 1606 (47.5) 523 (42.5) 756 (51.8) 327 (47.2)
  - Only TNF inhibitors: 12 (0.4) 1 (0.1) 10 (0.7) 1 (0.1)
  - Thiopurines and TNF inhibitors: 508 (15.0) 100 (8.1) 306 (21.0) 102 (14.7)
- At least one first degree relative with:
  - Cancer: 2781 (29.7) 1245 (31.3) 1303 (30.7) 233 (20.5)
  - Cancer before age 50: 1432 (15.3) 624 (15.7) 663 (15.6) 145 (12.8)
  - Cancer after age 50: 1349 (14.4) 621 (15.6) 640 (15.1) 88 (7.8)

IBD=inflammatory bowel disease; IQR=interquartile range; SD=standard deviation; TNF=tumour necrosis factor.

*Coverage of thiopurines and adalimumab in the registers is virtually complete, but infliximab has a national coverage of only 30-40% (coverage of all anti-TNF drugs is approximately 70%), which is why it is possible that some patients had only been exposed to infliximab and were hence misclassified.
Table 4 | Absolute incidence rates per 1000 person years (95% confidence intervals) of all cause cancer in incident cases of patients with childhood onset (≤18 years) inflammatory bowel disease and matched general population reference individuals from 1964-2014 (first year of follow-up included)

| Event | Incidence rate (95% CI) |
|-------|-------------------------|
| Total people | 9405 | 4648 | 3768 | 989 | 92 |
| Person years | 148.62 | 77.66 | 57.60 | 13.67 | 1.86 |

Incidence rate started at the date of the first corresponding entry in the register for these analyses.

*Patients diagnosed more recently are much younger at end of follow-up than those diagnosed earlier, which will affect incidence rates as well as hazard ratios.

IBD = inflammatory bowel disease; NA = not applicable; TNF = tumour necrosis factor

| Age of first inflammatory bowel disease diagnosis (years) | Female | Male |
|--------------------------------------------------------|--------|------|
| <10 | 2.8 (2.5 to 3.2) | 3.5 (3.0 to 4.1) |
| <15 | 2.8 (2.4 to 3.1) | 3.2 (2.7 to 3.8) |
| <17 | 3.1 (2.8 to 3.5) | 3.8 (3.3 to 4.3) |
| <18 | 3.3 (3.0 to 3.7) | 3.9 (3.4 to 4.3) |

Sex:

**Age of first inflammatory bowel disease diagnosis:**

- **1964-1979:** 4.6 (4.0 to 5.4) |
- **1980-89:** 3.6 (3.0 to 4.2) |
- **1990-2001:** 3.1 (2.6 to 3.7) |
- **2002-14:** 1.8 (1.4 to 2.4) |

**Complications during follow-up:**

| Complication | Event |
|--------------|-------|
| Extra intestinal manifestations | 7.7 (5.5 to 10.8) |
| Primary sclerosing cholangitis | 12.8 (10.2 to 16.0) |

**Colitis during follow-up:**

| Colitis | Event |
|---------|-------|
| ≤10 years | 9.4 (7.5 to 11.7) |
| ≤15 years | 5.0 (4.4 to 5.7) |
| ≤17 years | 4.1 (3.2 to 5.2) |

| Surgery for inflammatory bowel disease: | Event |
|----------------------------------------|-------|
| Bowel surgery | 5.0 (4.4 to 5.6) |
| Perianal surgery | 4.3 (3.2 to 5.2) |

**Drugs for inflammatory bowel disease:**

| Drugs for inflammatory bowel disease: | Event |
|-------------------------------------|-------|
| Immunosuppressives or TNF inhibitors | 1.0 (0.5 to 2.3) |
| Only thiopurines | 0.9 (0.2 to 3.5) |

**At least one first degree relative with:**

| Cancer | Event |
|--------|-------|
| Cancer before age 50 years | 4.1 (3.4 to 4.7) |
| Cancer before age 50 years | 4.0 (3.4 to 4.7) |

**Relative hazard ratios:**

- **Colitis and colonic inflammation in Crohn’s disease:**
  - Patients with ulcerative colitis were at higher risk of colorectal cancer (33.3, 23.1 to 49.1) than patients with Crohn’s disease (5.8, 3.2 to 10.4, P=0.001).
- **Hazard ratio for colorectal cancer in the first 20 years of follow-up** was considerably lower in childhood-onset inflammatory bowel disease than in disease with onset at other ages (supplementary fig S2).
Fig 2 | Adjusted* hazard ratios for all cancers during all available follow-up in patients with childhood onset (<18 years) inflammatory bowel disease and matched general population comparators in 1964-2014 (first year of follow-up included). Numbers in the figure represent cancers in patients with inflammatory bowel disease, and forest plots represent hazard ratio (95% confidence interval). Follow-up of extra-intestinal manifestations, primary sclerosing cholangitis, colitis during follow-up, and surgery started at the first date of the corresponding register entry. Follow-up of colitis ≥10 years before start of follow-up started 10 years after the first diagnostic listing of colitis.

*For sex, age at diagnosis, calendar year at diagnosis, and county.

Cancer occurring before age 18 and trends over time
All cancer specific analyses were also stratified by age at the time of cancer diagnosis (all ages, <18, ≥18) and calendar period of disease onset (supplementary tables S10a-d). In a sensitivity analysis, we performed all cancer subtype analyses excluding the first year of follow-up (during which eight cases of cancer occurred), which resulted in almost identical overall hazard ratios (supplementary table S10d).

Restricting our analyses to cancers occurring before 18 years of age, we found 20 cancers in 9405 cases of childhood onset inflammatory bowel disease followed for 34 907 person years (0.6 per 1000 person years, 95% confidence interval 0.4 to 0.9) and 73 cancers in 92 870 matched reference individuals followed for 346 526 person years (0.2 per 1000 person years, 0.2 to 0.3). These absolute rates corresponded to one extra case of cancer in childhood for every 2500 children with inflammatory bowel disease followed for a year. Only 0.2% (1 in 500) of patients with childhood onset inflammatory bowel disease or Crohn’s disease (supplementary table S10a-c). Of the 24 lymphoid neoplasms identified, five were Hodgkin lymphomas, two were acute lymphoblastic leukaemias, and 17 were non-Hodgkin lymphomas (nine B cell lymphomas, six lymphomas not otherwise specified, and two T cell lymphomas). The two T cell lymphomas occurred in one patient who was 60 years at the time of the cancer (not exposed to thiopurines or TNF inhibitors in the last nine years before cancer) and in one boy who was 15 years at the time of cancer and who had been exposed to thiopurine but not to a TNF inhibitor.

Patients with inflammatory bowel disease were at increased risk of both melanoma (1.7, 1.2 to 2.4) and non-melanoma skin cancer (5.9, 3.6 to 9.5, supplementary tables S10a-c). Childhood onset inflammatory bowel disease was not associated with a significantly lower risk of any type of cancer, although the hazard ratio for breast cancer was only 0.8 (0.5 to 1.2).
inflammatory bowel disease will develop cancer in childhood (supplementary table S8a). The restriction to cancers in patients <18 years of age showed hazard ratios similar to those for all available follow-up periods (fig 5, supplementary fig S3, supplementary tables S9a-d, and supplementary tables S10a-d).

Risk of cancer before the 18th birthday was similar between calendar periods (1964-2001 and 2002-14) for all cancer, gastrointestinal cancer, colorectal cancer, and lymphoid neoplasms (supplementary tables S10a-d). Hazard ratios for all cancer before the 25th birthday were also stable over calendar periods (1964-1989: 1.6, 1.0 to 2.4; 1990-2001: 2.3, 1.5 to 3.3; 2002-06: 2.9, 1.9 to 4.2; 2007-14: 2.2, 1.1 to 4.2; supplementary table S10e).

**Discussion**

**Main findings**

This nationwide population based study of more than 9000 people with childhood onset inflammatory bowel disease found an increased risk of cancer compared with reference individuals without inflammatory bowel disease. Relative risks for gastrointestinal cancers were high, but absolute risks were low. The risk of any cancer remained high beyond five years of follow-up. We found that primary sclerosing cholangitis, longstanding colitis, and a family history of any cancer in relatives <50 years of age were also risk factors for any cancer in childhood onset inflammatory bowel disease, which is in line with earlier reports in adult onset disease.

**Comparison with previous studies**

In two American studies of childhood onset inflammatory bowel disease (1919-65), with onset of ulcerative colitis before age 14 and onset of Crohn's disease before age 22, patients were followed for a maximum of 43 years. Of 396 patients with ulcerative colitis, 53 developed cancer, and the 35 year risk of cancer was 43%. Of 449 patients with Crohn's disease followed for 7077 person years, eight developed colorectal cancer, corresponding to 20 times more cases than expected. In a Scottish study from 1973 that followed 25 children with ulcerative colitis for 303 person years, only one (4%) developed cancer.

In a Swedish population based study from 1990, Ekbom et al reported 13 cases of colorectal cancer in all Swedish inpatients diagnosed as having ulcerative colitis before they were 15. This corresponds to three cases per 1000 person years, a severalfold increased risk. In a similar study in patients with Crohn's disease the authors reported the relative risk of colorectal cancer in children and young adults (<30 years). They found five cases of cancer in 12000 person years, corresponding to an estimated relative risk of 9.5 (3 to 23). One of the few recent studies on childhood onset inflammatory bowel disease reported a very high relative risk of colorectal cancer in ulcerative colitis (44, 27 to 71) and a lower risk in Crohn's disease (2, 0.3 to 17). But the small number of events led to wide confidence intervals; only one child with Crohn's disease developed colorectal cancer.
The excess risk was mainly due to an increased risk of cancer. We found an excess risk also in children with disease, especially ulcerative colitis and colorectal cancer, which has shown an association between inflammatory bowel disease and colorectal cancer was common (40% of cancers). Our study also showed that gastrointestinal cancer was common (40% of cancers) of gastrointestinal cancer. In contrast to several studies of adult inflammatory bowel disease, we found no trends indicating a fall in colorectal cancer or cancer overall in inflammatory bowel disease in recent years.

We also examined the risk of lymphoid neoplasms in childhood onset inflammatory bowel disease. A previous US study only included two lymphomas despite 30 years of follow-up. The two cases

| Total Follow-up (years) | Inflammatory bowel disease | Ulcerative colitis | Crohn’s disease | IBD unclassified |
|------------------------|----------------------------|--------------------|-----------------|-----------------|
| 0 to ≤1                | 20                         | 9                  | 9               | 2               |
| 1 to ≤5                | 8                          | 4                  | 3               | 1               |
| ≥5                     | 6                          | 2                  | 4               | 0               |

| Gender                  | Boys                        | Girls              |                |
|-------------------------|------------------------------|--------------------|----------------|
|                         | 10                           | 10                 |                |

| Age at first diagnosis of inflammatory bowel disease (years) | Inflammatory bowel disease | Ulcerative colitis | Crohn’s disease | IBD unclassified |
|------------------------------------------------------------|----------------------------|--------------------|-----------------|-----------------|
| <10                                                        | 9                          | 5                  | 3               | 1               |
| ≥10 to <17                                                | 9                          | 2                  | 6               | 1               |
| <18                                                       | 20                         | 9                  | 9               | 2               |

| Year of first diagnosis of inflammatory bowel disease       | Inflammatory bowel disease | Ulcerative colitis | Crohn’s disease | IBD unclassified |
|------------------------------------------------------------|----------------------------|--------------------|-----------------|-----------------|
| 2002-14                                                    | 9                          | 2                  | 5               | 2               |
| 1990-2001                                                  | 4                          | 1                  | 3               | 0               |
| 1980-89                                                    | 3                          | 3                  | 0               | 0               |
| 1964-79                                                    | 4                          | 3                  | 1               | 0               |

| Complications during follow-up                          | Inflammatory bowel disease | Ulcerative colitis | Crohn’s disease | IBD unclassified |
|----------------------------------------------------------|----------------------------|--------------------|-----------------|-----------------|
| Extra-intestinal manifestations                          | 1                          |                    | 1               |                 |
| Primary sclerosing cholangitis                           | 1                          |                    | 1               |                 |

| Colitis                                                  | Inflammatory bowel disease | Ulcerative colitis | Crohn’s disease | IBD unclassified |
|----------------------------------------------------------|----------------------------|--------------------|-----------------|-----------------|
| Colitis ≥10 years                                        | 0                          |                    | 0               |                 |
| Colitis during follow-up                                 | 5                          | 3                  | 2               | 0               |

| Surgery                                                  | Inflammatory bowel disease | Ulcerative colitis | Crohn’s disease | IBD unclassified |
|----------------------------------------------------------|----------------------------|--------------------|-----------------|-----------------|
| Bowel surgery                                            | 5                          | 4                  | 2               | 0               |
| Perianal surgery                                         |                            |                    |                 |                 |

| More than one first degree relative with                 | Inflammatory bowel disease | Ulcerative colitis | Crohn’s disease | IBD unclassified |
|----------------------------------------------------------|----------------------------|--------------------|-----------------|-----------------|
| Cancer before age 50                                     | 3                          | 2                  | 0               | 1               |
| Cancer after age 50                                      | 1                          |                    | 1               | 0               |

Fig 5 | Adjusted* hazard ratios for all cancer occurring before the 18th birthday in patients with childhood onset (≤18 years) inflammatory bowel disease and matched general population comparators 1964-2014 (first year of follow-up included). Numbers next to the forest plot represent the number of cancers in patients with inflammatory bowel disease, hazard ratios, and 95% confidence intervals. Follow-up of extra-intestinal manifestations, primary sclerosing cholangitis, colitis during follow-up, and surgery started at the first date of the corresponding register entry. Follow-up of colitis ≥10 years before start of follow-up started 10 years after the first diagnostic listing of colitis. *For sex, age at diagnosis, calendar year at diagnosis, and county.

Our risk estimates for cancer overall are similar to those in a recent Danish study by Kappelman et al (table 1). The excess risk was mainly due to an increased risk of gastrointestinal cancer. Our study also showed that gastrointestinal cancer was common (40% of cancers) in childhood onset inflammatory bowel disease, with high relative risk estimates. Many studies have shown an association between inflammatory bowel disease, especially ulcerative colitis and colorectal cancer. We found an excess risk also in children with Crohn’s disease. In the 3380 people with childhood onset ulcerative colitis the adjusted hazard ratio for colorectal cancer was 33.3 (23.1 to 49.1); in Crohn’s disease the adjusted hazard ratio for colorectal cancer was 5.8 (3.2 to 10.4). Colorectal cancer is a major cause of cancer mortality in the population and even a moderately increased incidence is likely to have a large effect on patients with inflammatory bowel disease. In contrast to several studies of adult inflammatory bowel disease, we found no trends indicating a fall in colorectal cancer or cancer overall in inflammatory bowel disease in recent years.

Kappelman et al reported a relative risk of small bowel adenocarcinoma in patients with inflammatory bowel disease of 67, and a later meta-analysis of 9642 patients with Crohn’s disease showed a 28-fold risk of small bowel adenocarcinoma in patients with Crohn’s disease. A more recent US case-control study reported an odds ratio of 12 for small bowel adenocarcinoma in patients with Crohn’s disease.

These findings are in line with our results (hazard ratio 12.8, 3.4 to 51.8), based on five cases of small bowel adenocarcinoma since 1964, four of which occurred in adulthood.

We also examined the risk of lymphoid neoplasms in childhood onset inflammatory bowel disease. A previous US study only included two lymphomas despite 30 years of follow-up. The two cases...
corresponded to a non-significant standardised incidence ratio of 7.5, but the confidence interval was wide (0.7 to 42.0). Further, all patients originated from a tertiary centre, so true lymphoma risk might have been overestimated. By contrast, we found a 2.7-fold risk of lymphoid neoplasms (1.7 to 4.2) in childhood onset inflammatory bowel disease (restricting the study to patients diagnosed in 2002-14, the hazard ratio was 2.6, 0.9 to 6.5) based on 24 lymphomas. The relative risks of lymphoma were similar in ulcerative colitis and Crohn’s disease and remained significantly increased even when all lymphomas occurring within the first year of follow-up were excluded. The risk increase is noteworthy because a meta-analysis of population based cohort studies on adult inflammatory bowel disease and lymphoma found no excess risk.\(^4\) de Ridder et al\(^25\) surveyed paediatric gastroenterologists in 20 European countries and Israel and found 18 cases of cancer. Haematopoietic cancers dominated (11 cases, three of which were T cell lymphomas), but the denominator was unknown, so the study could not present any absolute or relative risk estimates. In our study only two cases of T cell lymphoma occurred among 9405 patients with childhood onset inflammatory bowel disease (0.02%) followed for 148,682 person years (0.01 per 1000 person years), of which only one occurred in childhood. In other words, T cell lymphomas are extremely rare, even after the introduction of thiopurines and biological agents.

Recent data have shown increased risk of lymphoma in adult patients with inflammatory bowel disease who are currently taking thiopurine (standardised incidence ratio 5.7, 3.1 to 7.8) compared with former thiopurine users (1.4, 0.9 to 2.3). Men aged <30 years had the highest relative risk of lymphoma (7.0, 3.0 to 16.4).\(^10\) In a subanalysis we examined the risk of any cancer stratified by medical treatment in 3383 patients with a diagnosis of inflammatory bowel disease after the start of the Swedish Prescribed Drug Register (1 July 2005). In this young age group confidence intervals were wide and overlapping with no clear differences between groups based on 21 first cancers. This is in line with another study of 5766 cases of childhood onset inflammatory bowel disease mainly from tertiary paediatric centres in the USA and Europe followed for a median of 4.7 years—15 first malignancies were diagnosed, nine of which were lymphoid neoplasms.\(^5\) Confidence intervals in this study were also wide, and no significant differences between groups could be identified. Our study was underpowered with regard to drug exposures (supplement 13), and we were only able to identify about 70% of all patients taking TNF inhibitors, which might also have affected the results. To confidently elucidate the importance of drugs for cancer development in young patients, we need time dependent analyses of drug exposures that also have the power to take disease phenotype into account.

Our study confirms reports that primary sclerosing cholangitis is a risk factor for cancer in inflammatory bowel disease.\(^56\) It adds to previous literature in calculating a precise risk estimate in children with inflammatory bowel disease. More than 700 patients with inflammatory bowel disease in our study had a diagnosis of primary sclerosing cholangitis, which corresponds to 7% of patients with inflammatory bowel disease (11% in ulcerative colitis and 3% in Crohn’s disease). Our study also found that patients with a family history\(^4\) of early cancer (<50 years) had a higher relative risk of cancer in childhood onset inflammatory bowel disease.

**Strengths and limitations**

One strength of the study is the large number of participants, which enabled us to stratify for both sex and calendar period. Earlier data have indicated that cancer in inflammatory bowel disease might differ by sex\(^5\) and that relative risks have decreased over time.\(^6\) Another strength is the virtually complete follow-up regarding cancer. The Swedish Cancer Register was established in 1958, and a recent validation of the register found a completeness of >96%.\(^3\) Furthermore, we used matched reference individuals from the general population, enabling us to adjust for important potential confounders. These data were obtained from the Swedish Patient Register, which has nationwide follow-up since 1987.\(^33\) We recently performed a validation study in the Swedish patient register and found a positive predictive value for a diagnosis of inflammatory bowel disease of 93%.\(^39\) Our study included >4600 patients who received a diagnosis of childhood onset inflammatory bowel disease since 2002. Medical and surgical management, including surveillance guidelines, has changed in the past two decades, and this is likely to reflect on cancer risk estimates. We found similar or higher cancer risks in patients diagnosed in 2002-14 than in those with a diagnosis until 2001.

One limitation of the study is that nationwide registers do not contain information on smoking. Smoking is well known to protect from ulcerative colitis and increase the risk of Crohn’s disease\(^5\) and many cancers.\(^5\) Because the vast majority of the study population was probably not smoking at the age of their first inflammatory bowel disease diagnosis (http://www.can.se/Publikationer/rapporter/skolelevers-drogvanor-2015/), and because patients already diagnosed with inflammatory bowel disease are unlikely to start smoking to a higher degree than the general population, smoking is unlikely to be a significant confounder of our results. Furthermore, patients with both ulcerative colitis and Crohn’s disease had a higher risk of malignancy, and patients with ulcerative colitis (supposedly more often non-smokers) had the highest risk for cancer.

We did not have detailed information on disease severity, disease extent, or disease behaviour in our study population. We used ICD codes recorded prospectively in clinical practice as proxies for disease extent and disease behaviour, using the Paris classification.\(^40\) We have not yet validated the use of ICD codes for disease extent and behaviour in clinical practice and urge caution when interpreting these results. Finally, we had limited power to assess certain...
types of cancer (partly because of limited follow-up). The median age at the end of follow-up in our cohort was 27 years.

Mechanisms and clinical implications

The increased risk of cancer in childhood onset inflammatory bowel disease is likely to have several explanations. Although the higher risk in the first year of follow-up indicates a degree of detection and surveillance bias, this is unlikely to have more than a marginal role in the risk of cancer more than five years after diagnosis. Even then, patients were at a more than twofold risk of cancer. Patients with inflammatory bowel disease have regular endoscopies, which might result in earlier detection of some intestinal cancers (such as colorectal cancer) and might have further increased the incidence rate of such cancers in the inflammatory bowel disease population.

We cannot rule out that thiopurines or TNF inhibitors increase the risk of cancer, as our study was not big enough to recognise whether drugs are a major risk factor for cancer development in children and young adults. Instead, we suggest that extent and duration of chronic inflammation might be the main driving mechanisms underlying the increased risk of cancer.55 We found no decreased risk of cancer overall (before the 25th birthday) since the introduction of thiopurines or biological therapies. Over the same time period, colectomy rates seem to have fallen,20 which might partly explain why cancer rates in inflammatory bowel disease were stable.

Finally, the difference in incidence of colorectal cancer between childhood onset inflammatory bowel disease and other ages of onset after the same number of years of follow-up is important. Our data indicate that age of onset should be considered when designing surveillance strategies or studies that aim to evaluate colorectal cancer surveillance strategies for patients with inflammatory bowel disease in the future. We do not think that the presented data warrants evidence based recommendations further than that, as the choice of surveillance strategy is dependent on several other factors that are not described in the present study, such as national endoscopy capacity, costs of endoscopy for society and the individual, and to what extent surveillance detects cancer earlier and increases survival in different age groups (for example, someone dying from colorectal cancer in their 40s will lose more life years than someone who dies from colorectal cancer in their 70s).

Conclusion

We found an increased risk of cancer in childhood onset inflammatory bowel disease in childhood and later in life, especially gastrointestinal cancer and lymphoid neoplasms. Primary sclerosing cholangitis, longstanding colitis, and a family history of any cancer in relatives <50 years of age were strong risk factors for any cancer in childhood onset inflammatory bowel disease. The risk of cancer has not decreased since the introduction of thiopurines or biological therapies. The cumulative incidence of colorectal cancer differs across different ages of disease onset. Future surveillance programmes need to take these findings into account.

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Data sharing: No additional data available due to Swedish regulation.

Transparency: The lead author (OO) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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1 Bernstein CN, Blanchard JF, Kliever E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer 2001;91:854-62. doi:10.1002/1053-0142(20010215)91:4<854::AID-CNCR1073>3.0.CO;2-Z
2 Goldacre MJ, Wotton CJ, Yeates D, Seagroatt V, Jewell D. Cancer in patients with ulcerative colitis, Crohn’s-disease and coeliac disease: record linkage study. Eur J Gastroenterol Hepatol 2008;20:397-304. doi:10.1097/MEG.0b013e3282f2a5e2
3 Beaugerie L, Srivast V, Sepsik S, et al. CESAME Study Group. Risk of colorectal high-grade dysplasia and cancer in a prospective observational cohort of patients with inflammatory bowel disease. Gastroenterology 2013;145:166-175.e8. doi:10.1053/j.gastro.2013.03.044
4 Asling J, Dickman PM, Karlén P, et al. Family history as a risk factor for colorectal cancer in inflammatory bowel disease. Gastroenterology 2001;120:1356-62. doi:10.1053/gast.2001.24057
5 Soetikno RM, Lin OS, Heidenreich PA, Young HS, Blackstone MO. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis. Gastrointest Endosc 2002;56:48-54. doi:10.1067/mge.2002.125367
6 Jess T, Simonsen J, Jørgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. Gastroenterology 2012;142:375-81. doi:10.1053/j.gastro.2012.04.016
7 Malmborg P, Grahnquist I, Idström M, et al. Presentation and progression of childhood-onset inflammatory bowel disease in Northern Stockholm County. Inflamm Bowel Dis 2015;21:1098-108. doi:10.1097/MIB.0000000000000356
8 Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology 2008;135:1114-22. doi:10.1053/j.gastro.2008.06.081
9 Gower-Rousseau C, Dauchet L, Vernier-Massouille G, et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. Am J Gastroenterol 2009;104:2080-8. doi:10.1038/ajg.2009.177
10 Vernier-Massouille G, Balde M, Salleron J, et al. Natural history of pediatric Crohn’s disease: a population-based cohort study. Gastroenterology 2008;135:1106-13. doi:10.1053/j.gastro.2008.06.079
11 Haukka J, Voutilainen S, et al. Natural history of Crohn’s disease: comparison between childhood- and adult-onset disease. Inflamm Bowel Dis 2010;16:953-61. doi:10.1002/ibd.21152
12 Devroede G, Taylor WF, Sauer WG, Jackman RJ, Stackler GB. Cancer risk and life expectancy of children with ulcerative colitis. N Engl J Med 1971;285:17-21. doi:10.1056/NEJM197102122850103
13 Weedon DD, Shorter RG, Istrup DM, Huizenga KA, Taylor WF. Crohn’s disease and cancer. N Engl J Med 1973;289:1099-103. doi:10.1056/NEJM19731122289121
14 Goel KM, Shanks RA. Long-term prognosis of children with ulcerative colitis. Arch Dis Child 1973;48:337-42. doi:10.1136/adc.48.5.337
15 Ekbohm A, Helmic K, Zach M, Adamo HO. Ulcerative colitis and colorectal cancer. A population-based study. N Engl J Med 1990;323:1228-33. doi:10.1056/NEJM199010313231802
16 Pienne A, Savoye G, Turt C, et al. Mortality and cancer in pediatric-onset inflammatory bowel disease: a population-based study. Am J Gastroenterol 2010;105:1647-53. doi:10.1111/j.1572-0241.2009.03052.x
17 Hyams JS, Dubinsky MC, Baldassano RN, et al. Infliximab is not associated with increased risk of malignancy or hemophagocytic lymphohistiocytosis in pediatric inflammatory bowel disease. Gastroenterology 2017;152:1901-14.e3. doi:10.1053/j.gastro.2017.02.004
18 Benchimol EI, Fortin PJ, Gozdzik P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. Inflamm Bowel Dis 2011;17:423-39. doi:10.1002/ibd.21349
19 Neovius M, Fink FY, Grahnquist L, Lindholm J, Ekbohm A, Askling J. Changing pattern of paediatric inflammatory bowel disease in northern Stockholm 1990-2001. Gut 2003;52:1432-6. doi:10.1136/gut.52.14.1432
20 Askling J. Changing pattern of paediatric inflammatory bowel disease: a systematic review of international trends. Inflamm Bowel Dis 2017;23:216-21. doi:10.1097/MIB.0000439066.69340.3c
21 Pedersen PB, Brunmark A, Søgaard K, et al. Mortality and cancer in patients with inflammatory bowel disease: a nationwide population-based cohort study with 30 years of follow-up evaluation. Scand J Gastroenterol 2018;53:1286-95. doi:10.1080/00365520.2018.1457574
22 Neovius M, Sundström A, Simard J, et al. ARTIS Study Group. Small-area variations in sales of TNF inhibitors in Sweden between 2000 and 2009. Scand J Rheumatol 2011;40:8-15. doi:10.3109/030093710.2010.493895
23 Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis 2011;17:1314-21. doi:10.1007/s10050-011-1493
24 Neovius M, Sundström A, Bimel D, et al. Risk of cancer in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. Clin Gastroenterol Hepatol 2013;11:1561-70. doi:10.1016/j.cgh.2013.06.023
25 Ludvigsson JF, Hålborg SE, Krudop G, et al. Mortality and experience from the first six months. Inflamm Bowel Dis 2010;16:726-35. doi:10.1002/ibd.20129
26 Ludvigsson JF, Andersson E, Ekbohm A, et al. External validation and review of the Swedish national inpatient register. BMC Public Health 2011;11:450. doi:10.1186/1471-2458-11-450
27 Barlow L, Westergren K, Holmberg L, Talbäck M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol 2009;48:27-33. doi:10.1080/02841070802476644
28 de Faire U, Frigbert L, Lorch U, Lundman T. A validation of cause-of-death certification in 1,156 deaths. Acta Med Scand 1976;200:223-6. doi:10.1111/j.1600-0463.1976.tb03821.x
29 Busch K, Ludvigsson JF, Ekström-Smedby K, Ekbohm A, Askling J, Neovius M. Nationwide prevalence of inflammatory bowel disease in Sweden: a population-based register study. Aliment Pharmacol Ther 2014;39:57-68. doi:10.1111/apt.13258
30 Ludvigsson JF, Busch K, Ölfen O, et al. Prevalence of paediatric inflammatory bowel disease in the Swedish population: a population-based register study. BMC Gastroenterol 2017;17:23. doi:10.1186/s12876-017-0578-9
31 Lophaven SN, Lyngé E, Burisch J. The incidence of inflammatory bowel disease in Denmark 1980-2013: a nationwide population-based study. Aliment Pharmacol Ther 2017,65:961-72. doi:10.1111/apt.14371
32 Jakobsen GL, Sternejårg EC, Øien O, et al. Validating inflammatory bowel disease (inflammatory bowel disease) in the Swedish National Patient Register and the Swedish Quality Register for inflammatory bowel disease (SWIBREG). Scand J Gastroenterol 2017;52:216-21. doi:10.1080/030036521.2016.1246605
33 Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis 2011;17:1314-21. doi:10.1007/s10050-011-1493
34 Neovius M, Sundström A, Simard J, et al. ARTIS Study Group. Small-area variations in sales of TNF inhibitors in Sweden between 2000 and 2009. Scand J Rheumatol 2011;40:8-15. doi:10.3109/030093710.2010.493895
35 Ekbom A. The Swedish multi-generation Register. Methods Mol Biol 2011;767:215-20. doi:10.1007/978-1-59745-428-0_10
36 Ludvigsson JF, Hålborg SE, Krudop G, et al. Ethical aspects of registry-based research in the Nordic countries. Clin Epidemiol 2015;7:491-508. doi:10.2147/CLEP.S90589
37 Ribot D. The risk of ulcerative colitis in Europe: a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2011;20:1120-3. doi:10.1158/1055-9965.EPI-10-1281
38 Pedersen N, Duricova D, Ekljær M, Gamborg M, Munkholm P, Jess T. Risk of extra-intestinal cancer in inflammatory bowel disease: meta-analysis of population-based cohort studies. Am J Epidemiol 2014;179:1343-53. doi:10.1093/aje/kwu185
39 Kottaridou M, Lewis JD, Beutler E, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. Clin Gastroenterol Hepatol 2015;13:847-58.e4. doi:10.1016/j.cgh.2014.05.015
40 Rubin DT, Hsu D, Kinnuncar JA, et al. Inflammation is an independent risk factor for colorectal neoplasia in patients with ulcerative colitis: a case-control study. Gastroenterology 2014;146:1601-8. e1-4. doi:10.1053/j.gastro.2013.06.023
41 Söderlund V, Granath F, Brolström O, et al. Inflammatory bowel disease confers a lower risk of colorectal cancer to females than males. Gastroenterology 2010;138:1697-703. doi:10.1053/j.gastro.2010.02.007
42 Mahad SS, Minor KS, Sore R, Hornung CA, Galanduk S. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc 2006;81:1462-71. doi:10.4065/mcp.2006.06.13
54 Agudo A, Bonet C, Travier N, et al. Impact of cigarette smoking on cancer risk in the European prospective investigation into cancer and nutrition study. *J Clin Oncol* 2012;30:4550-7. doi:10.1200/JCO.2011.41.0183

55 Nieminen U, Jussila A, Nordling S, Mustonen H, Färkkilä MA. Inflammation and disease duration have a cumulative effect on the risk of dysplasia and carcinoma in inflammatory bowel disease: a case-control observational study based on registry data. *Int J Cancer* 2014;134:189-96. doi:10.1002/ijc.28346

**Supplementary information:** STROBE statement, supplementary tables S1-S7, supplements 12 and 13

**Supplementary information:** Supplementary figures S1 and S2, supplementary tables S10a-e and S11

**Supplementary information:** Supplementary figure S3, supplementary tables S8-S9