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

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2017;358:j3951
http://dx.doi.org/10.1136/bmj.j3951

Accepted: 10 August 2017

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.

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.

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 cancer[4] 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,[6 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 cancer[23] and refer to adult guidelines regarding ulcerative colitis.[24]

Although colorectal cancer has been studied more than any other cancer in adult inflammatory

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)	NR	NA
Weedon,1973	USA 1919-65	<22 (mean 15)	449 (CD)	7077	12 (any cancer) 8 (CRC)	1.0 (0.5 to 2.1) for CRC	20 for CRC
Goel, 1973	Scotland 1931-71	<14 (mean 8)	25 (UC)	303	1 (CRC)	3.3 (0.2 to 16.3)	NR
Ekbom, 1990	Sweden 1945-83	<15	363 (UC)	4220	13 (CRC)	3.1 (1.7 to 16.3)	118 (63 to 202)
Ekbom, 1990	Sweden 1983-84	<30	964 (CD)	12 025	5 (CRC)	0.4 (0.2 to 0.9)	10 (3 to 23)
Ashworth, 2012	USA 1979-2009	<22 (mean 12)	839 (UC,CD)	4441	2 (lymphoma)	0.5 (0.1 to 1.5)	8 (0.7 to 42)
Jess, 2012	Denmark 1979-2008	<20	4763 (UC,CD)	52 100	18 (CRC)	0.3 (0.2 to 0.5)	UC: 44 (27 to 719) CD: 2 (0.3 to 17)
Peneau, 2013	France 1988-2009	<17 (median 14)	698 (UC,CD)	NR, median 12 years	9 (any cancer)	NR	3.0 (1.3 to 5.9)
de Ridder, 2014	Europe 2006-11	<19 (median 12)	NA	NA	18 (any cancer)	NA	NA
Kappelman, 2014	Denmark 1978-2010	<20	NR (UC,CD)	NR	NR	NR	UC: 2.0 (1.4 to 2.7) CD: 2.3 (1.5 to 3.4)
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)
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)‡ 0.6 (0.4 to 0.9)§	HR for any cancer: UC: 2.6 (2.3 to 3.0) CD: 1.7 (1.5 to 2.1) HR for CRC UC: 33 (23 to 49) CD: 5.8 (3.2 to 10)

CD=Crohn's disease; CI=confidence interval; CRC=colorectal cancer; HR=Hazard Ratio; NA=Not applicable; NR=not reported; thio=thiopurines; UC=ulcerative colitis.
*Standardised incidence ratio, unless otherwise stated
†Followed up until 23rd birthday
‡All follow-up
§Followed up until 18th birthday

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.[25] In a US study of 1374 children followed for 6624 patient years, only two children developed cancer (lymphoma),[26] 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.[27] Adult inflammatory bowel disease has been linked to an increased risk of malignant melanoma and non-melanoma skin cancer,[28 29] 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 in the Swedish Patient Register (which covers inpatient care 1964-2014 (nationwide since 1987) and non-primary outpatient care 2001-14) using the International Classification of Disease (ICD) codes listed in supplementary table S1. For the purpose of comparing cumulative incidence of colorectal cancer, we identified all cases of childhood onset and adult onset inflammatory bowel disease (supplementary figure S1).

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 registers[39] were confirmed to have inflammatory bowel disease when their medical

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).[39] 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 Register[31] (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 classification[40] 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),[41] 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 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.

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).

Table 2 | Baseline characteristics of all patients with childhood onset (<18 years) inflammatory bowel disease in Sweden 1964-2014 and reference individuals from the general population matched for sex, age, birth year, and place of residence. Numbers are n (%) unless otherwise stated.

Characteristic	Inflammatory bowel disease	Ulcerative colitis	Crohn's disease	IBD unclassified	Reference individuals
Total	9405	4648 (49.4)	3768 (41.1)	989 (10.5)	92 870
Female	4201 (44.7)	2121 (45.6)	1628 (43.2)	452 (45.7)	41 478 (44.7)
Male	5204 (55.3)	2527 (54.4)	2140 (56.8)	537 (54.3)	51 392 (55.3)
Age of first diagnosis or cohort entry (years)*					
Mean (SD)	14 (4)	14 (4)	14 (3)	14 (4)	14 (4)
Median (IQR)	15 (12-16)	14 (12-16)	15 (12-17)	15 (12-16)	15 (12-16)
<6	395 (4.2)	232 (5.0)	108 (2.9)	55 (5.6)	3919 (4.2)
<10	1332 (14.2)	747 (16.1)	434 (11.5)	151 (15.3)	13 187 (14.2)
<15	5174 (55.0)	2591 (55.7)	2050 (54.4)	533 (53.9)	51 160 (55.1)
<17	7821 (83.2)	3884 (83.6)	3116 (82.7)	821 (83.0)	77 261 (83.2)
<18	9405 (100)	4648 (100)	3768 (100)	989 (100)	92 870 (100)
Year of first diagnosis or cohort entry					
2002-14	4642 (49.4)	2077 (44.7)	1992 (52.9)	573 (57.9)	45 773 (49.3)
1990-2001	2363 (25.1)	1285 (27.6)	848 (22.5)	230 (23.3)	23 398 (25.2)
1980-89	1375 (14.6)	724 (15.6)	542 (14.4)	109 (11.0)	13 576 (14.6)
1964-1979	1025 (10.9)	562 (12.1)	386 (10.2)	77 (7.8)	10 123 (10.9)

*Fig 1 shows the distribution of age at first diagnosis.

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).

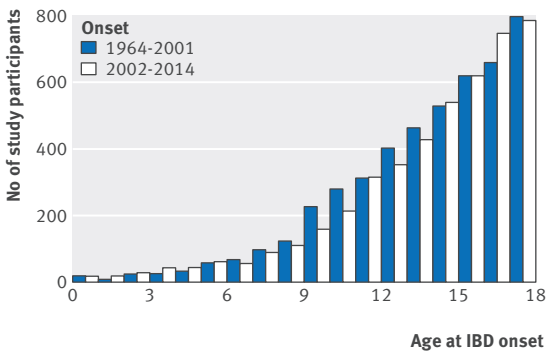

Fig 1 | Comparison of age at first visit or admission to hospital listing a diagnosis of inflammatory bowel disease between cohorts with onset in 1964-2001 and 2002-14. IBD=inflammatory bowel disease.

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

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)	944 (82.7)
≥30 to <45	2329 (24.8)	1140 (28.6)	1043 (24.4)	146 (12.8)
≥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):				
≥0 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)	281 (24.6)
≥20	2896 (30.8)	1343 (33.7)	1416 (33.1)	137 (12.0)
Maximum Paris endoscopy classification during follow-up:				
N Paris classified	NA	3651 (100)	4048 (100)	1106 (100)
E1 (proctitis)	NA	179 (4.9)	NA	45 (4.1)
E2 (left sided colitis)	NA	315 (8.6)	NA	77 (7.0)
E3E4 (total/pan colitis)	NA	2402 (65.8)	NA	504 (45.6)
EX (extent not defined)	NA	755 (20.7)	NA	480 (43.4)
L1 (terminal ileitis)	NA	NA	1103 (27.2)	NA
L2 (colonic)	NA	NA	1789 (44.2)	NA
L3LX (ileocecal or not defined)	NA	NA	1113 (27.5)	NA
B1 (non stricturing/penetrating)	NA	NA	3198 (79.0)	NA
B2 (stricturing)	NA	NA	373 (9.2)	NA
B3 (penetrating)	NA	NA	338 (8.3)	NA
B2B3 (stricturing and penetrating)	NA	NA	139 (3.4)	NA
P (perianal disease modifier)	NA	NA	780 (19.3)	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.

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); $P_{interaction}$=0.03), but this effect was not significant in Crohn's disease or inflammatory bowel disease overall ($P_{interaction}$=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 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)

	Inflammatory bowel disease	Ulcerative colitis	Crohn's disease	IBD unclassified	General population
Total people	9405	4648	3768	989	92870
Events	497	299	153	45	2256
Person years	148682	77646	57600	13437	1486983
Incidence rate	3.3 (3.1 to 3.7)	3.9 (3.4 to 4.3)	2.7 (2.3 to 3.1)	3.4 (2.5 to 4.5)	1.5 (1.5 to 1.6)
Years of follow-up:					
0 to <1	0.9 (0.4 -to 1.7)	0.9 (0.3 to 2.3)	0.8 (0.3 to 2.5)	1.0 (0.2 to 7.4)	0.2 (0.2 to 0.4)
1 to <5	0.5 (0.3 to 0.8)	0.4 (0.2 to 0.9)	0.7 (0.4 to 1.3)	0	0.3 (0.3 to 0.4)
≥5	4.5 (4.1 to 4.9)	5.1 (4.6 to 5.8)	3.5 (3.0 to 4.1)	4.8 (3.6 to 6.4)	2.0 (1.9 to 2.1)
Sex:					
Female	4.0 (3.5 to 4.5)	4.3 (3.6 to 5.0)	3.4 (2.8 to 4.2)	4.3 (2.9 to 6.2)	2.6 (2.5 to 2.7)
Male	2.8 (2.5 to 3.2)	3.5 (3.0 to 4.1)	2.1 (1.6 to 2.6)	2.5 (1.5 to 4.0)	0.6 (0.6 to 0.7)
Age of first inflammatory bowel disease diagnosis (years):					
<6	1.4 (0.7 to 2.9)	1.3 (0.5 to 3.1)	1.8 (0.5 to 7.2)	1.9 (0.3 to 13.5)	0.5 (0.3 to 0.7)
<10	2.1 (1.6 to 2.8)	2.0 (1.4 to 2.9)	2.4 (1.4 to 4.1)	2.1 (0.8 to 5.5)	0.8 (0.7 to 1.0)
<15	2.8 (2.4 to 3.1)	3.2 (2.7 to 3.8)	2.1 (1.6 to 2.7)	2.6 (1.7 to 4.1)	1.1 (1.1 to 1.2)
<17	3.1 (2.8 to 3.5)	3.8 (3.3 to 4.3)	2.3 (1.9 to 2.8)	2.8 (2.0 to 4.0)	1.4 (1.3 to 1.4)
<18	3.3 (3.01 to 3.7)	3.9 (3.4 to 4.3)	2.7 (2.3 to 3.1)	3.4 (2.5 to 4.5)	1.5 (1.5 to 1.6)
Year of first inflammatory bowel disease diagnosis:*					
2002-14	1.8 (1.4 to 2.4)	2.0 (1.4 to 2.9)	1.4 (0.9 to 2.3)	2.5 (1.3 to 5.1)	0.7 (0.6 to 0.8)
1990-2001	3.1 (2.6 to 3.7)	3.1 (2.5 to 3.9)	3.1 (2.3 to 4.1)	3.4 (2.0 to 5.8)	1.2 (1.1 to 1.3)
1980-89	3.6 (3.0 to 4.2)	4.3 (3.5 to 5.3)	2.7 (2.0 to 3.7)	2.9 (1.5 to 5.5)	1.6 (1.5 to 1.8)
1964-1979	4.6 (4.0 to 5.4)	5.5 (4.6 to 6.7)	3.3 (2.5 to 4.4)	4.6 (2.7 to 7.8)	2.4 (2.3 to 2.6)
Complications during follow-up:†					
Extra intestinal manifestations	7.7 (5.5 to 10.8)	10.4 (6.9 to 15.8)	3.7 (1.7 to 7.7)	13.4 (5.6 to 32.2)	NA
Primary sclerosing cholangitis	12.8 (10.2 to 16.0)	14.1 (11.1 to 18.1)	8.9 (4.42 to 17.7)	7.6 (2.9 to 20.2)	NA
Colitis during follow-up:†					
Colitis ≥10 years	9.4 (7.5 to 11.7)	10.4 (7.9 to 13.7)	7.9 (5.0 to 12.6)	7.6 (3.6 to 15.9)	NA
Colitis ever	5.0 (4.4 to 5.7)	5.8 (4.9 to 6.8)	4.0 (3.1 to 5.2)	3.6 (2.3 to 5.5)	NA
Surgery for inflammatory bowel disease:†					
Bowel surgery	5.0 (4.4 to 5.6)	6.8 (5.7 to 8.2)	3.4 (2.8 to 4.2)	7.7 (5.3 to 11.2)	NA
Perianal surgery	4.1 (3.2 to 5.2)	3.8 (2.5 to 5.9)	4.0 (2.9 to 5.5)	5.5 (2.9 to 10.5)	NA
Drugs for inflammatory bowel disease:†					
Incident cases from 1 July 2005	3383	1480	1435	468	NA
Never thiopurines or TNF inhibitors	1.0 (0.5 to 2.3)	1.6 (0.7 to 3.9)	0.5 (0.1 to 3.6)	0	NA
Only thiopurine	1.9 (1.1 to 3.3)	1.4 (0.5 to 3.7)	2.2 (1.1 to 4.7)	2.6 (0.6 to 10.2)	NA
Only TNF inhibitor	0	0	0	0	NA
Thiopurines and TNF inhibitors	0.9 (0.2 to 3.5)	0	0.8 (0.1 to 5.5)	4.0 (0.6 to 28.0)	NA
At least one first degree relative with:					
Cancer	4.0 (3.6 to 4.6)	4.5 (3.9 to 5.3)	3.4 (2.8 to 4.2)	4.0 (2.6 to 6.2)	NA
Cancer before age 50 years	4.1 (3.4 to 5.0)	5.1 (4.0 to 6.5)	3.3 (2.4 to 4.6)	2.7 (1.3 to 5.7)	NA
Cancer after age 50 years	4.0 (3.4 to 4.7)	4.2 (3.4 to 5.2)	3.5 (2.6 to 4.6)	5.3 (3.1 to 9.0)	NA

IBD=inflammatory bowel disease; NA=not applicable; TNF=tumour necrosis factor
*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.
†Follow-up started at the date of the first corresponding entry in the register for these analyses.

table S10a), most notably colorectal cancer (19.5, 14.7 to 26.2), small intestinal cancer (12.8, 3.4 to 51.8), and liver cancer (134, 59.6 to 382). Thus, the overall hazard ratio for gastrointestinal cancer in childhood onset inflammatory bowel disease was 18.0 (14.4 to 22.7).

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 to10.4, P<0.001, supplementary tables S10b-c). In a sensitivity analysis, we compared hazard ratios for colorectal cancer in patients with left sided or total colitis in ulcerative colitis and colonic inflammation in Crohn's disease. This restriction resulted in no statistical difference in relative risk between ulcerative colitis and Crohn's disease (P=0.13), but the decreased power precludes strong conclusions. In all patients, colorectal cancer was almost non-existent during the first five years of follow-up, but incidence was higher after 10 years of follow-up (supplementary table S11). The incidence of 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).

Patients with inflammatory bowel disease had an increased risk of lymphoid neoplasms compared with reference individuals (2.7, 1.7 to 4.2), both before and after the 18th birthday and for patients with ulcerative

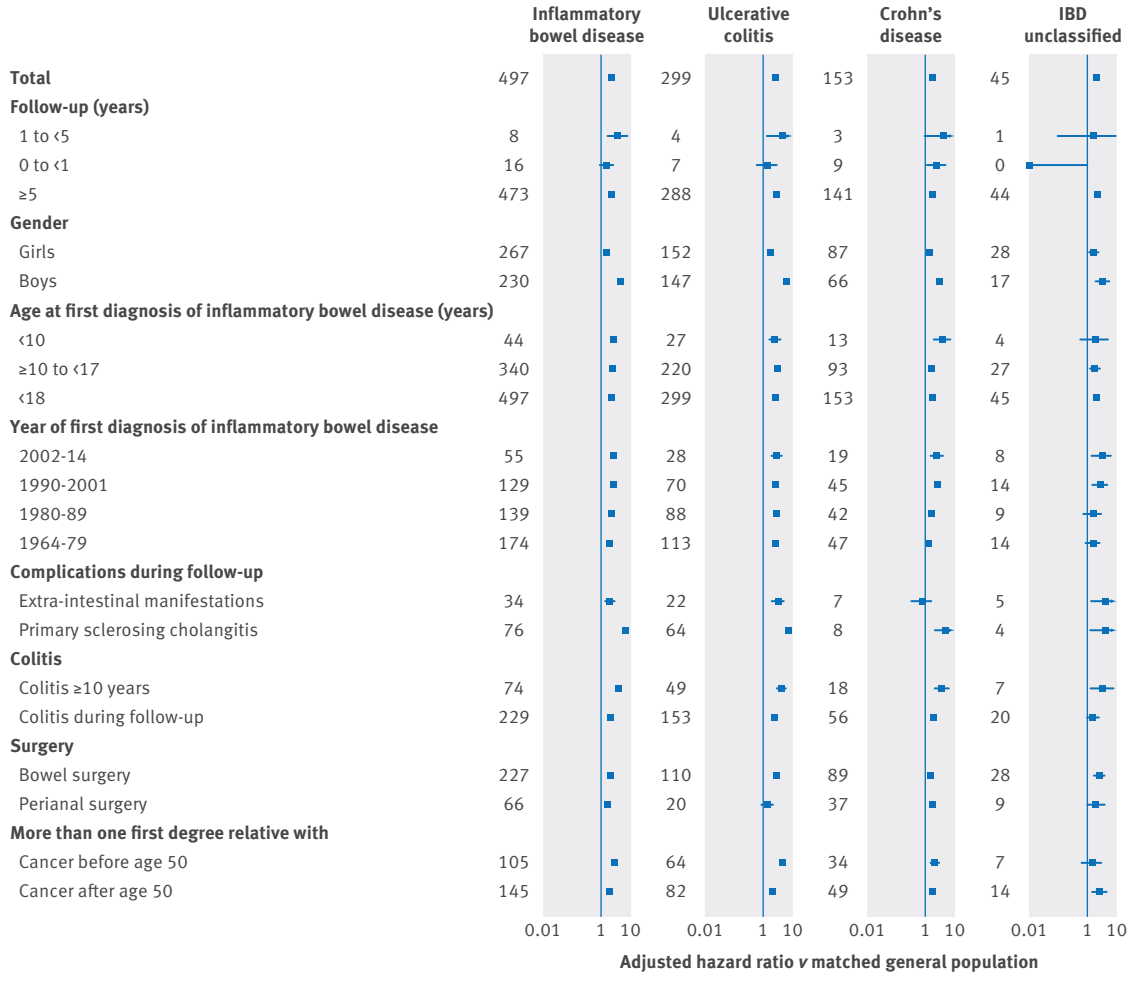

Fig 2 | Adjusted* hazard ratios for all cancers during all available follow-up in patients with childhood onset (<18 years) inflammatory bowel disease and matched general population comparators in 1964-2014 (first year of follow-up included). Numbers in the figure represent cancers in patients with inflammatory 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.

colitis 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).

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

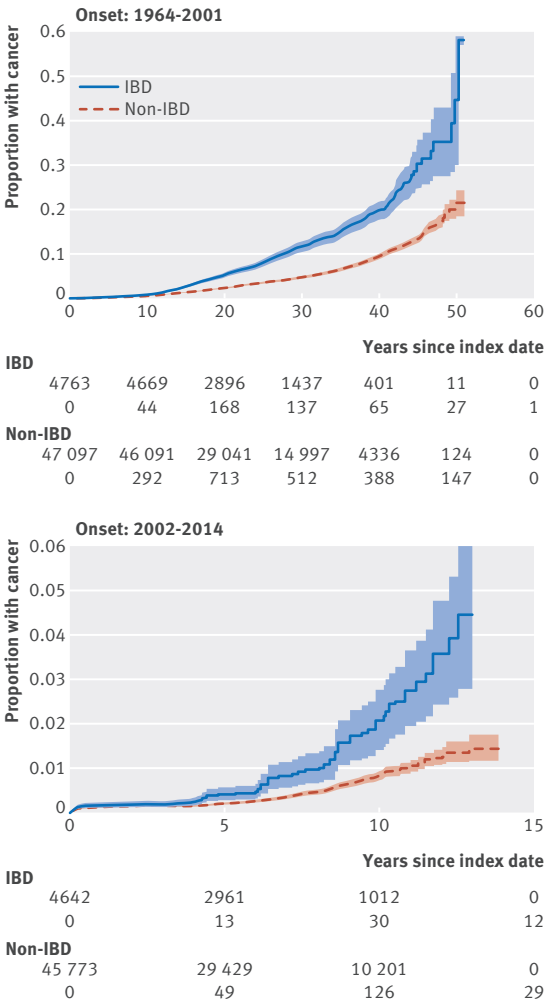

Fig 3 | Kaplan-Meier cumulative incidence curves with 95% confidence intervals showing the proportion of patients at risk of cancer after index date by calendar period of onset. The numbers show the number at risk (top) and the number of events since the previous data point (bottom) by inflammatory bowel disease status. IBD=inflammatory bowel disease.

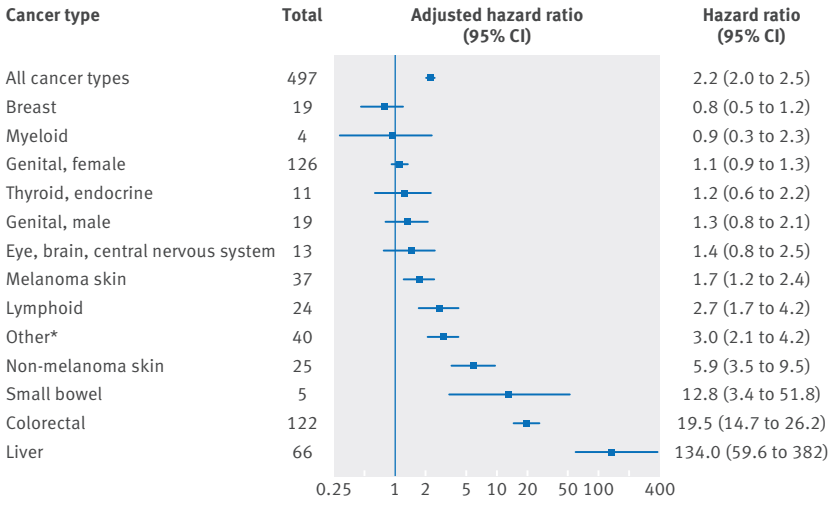

Fig 4 | Adjusted† hazard ratios of first ever event of a cancer in the cohort of patients with childhood onset (<18 year) inflammatory bowel disease during all available follow-up, compared with matched reference individuals from the general population (1964-2014), including first year of follow-up. Numbers next to the forest plot represent the number of cancers in patients with inflammatory bowel disease, hazard ratios, and 95% confidence intervals. *Other cancers are all cancer types not listed separately. †For sex, age at diagnosis, calendar year at diagnosis, and county

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.[3 4 5]

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%.[12] 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.[14]

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.[15] 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).[44] They found five cases of cancer in 12 000 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).[6] But the small number of events led to wide confidence intervals; only one child with Crohn's disease developed colorectal cancer.[6]

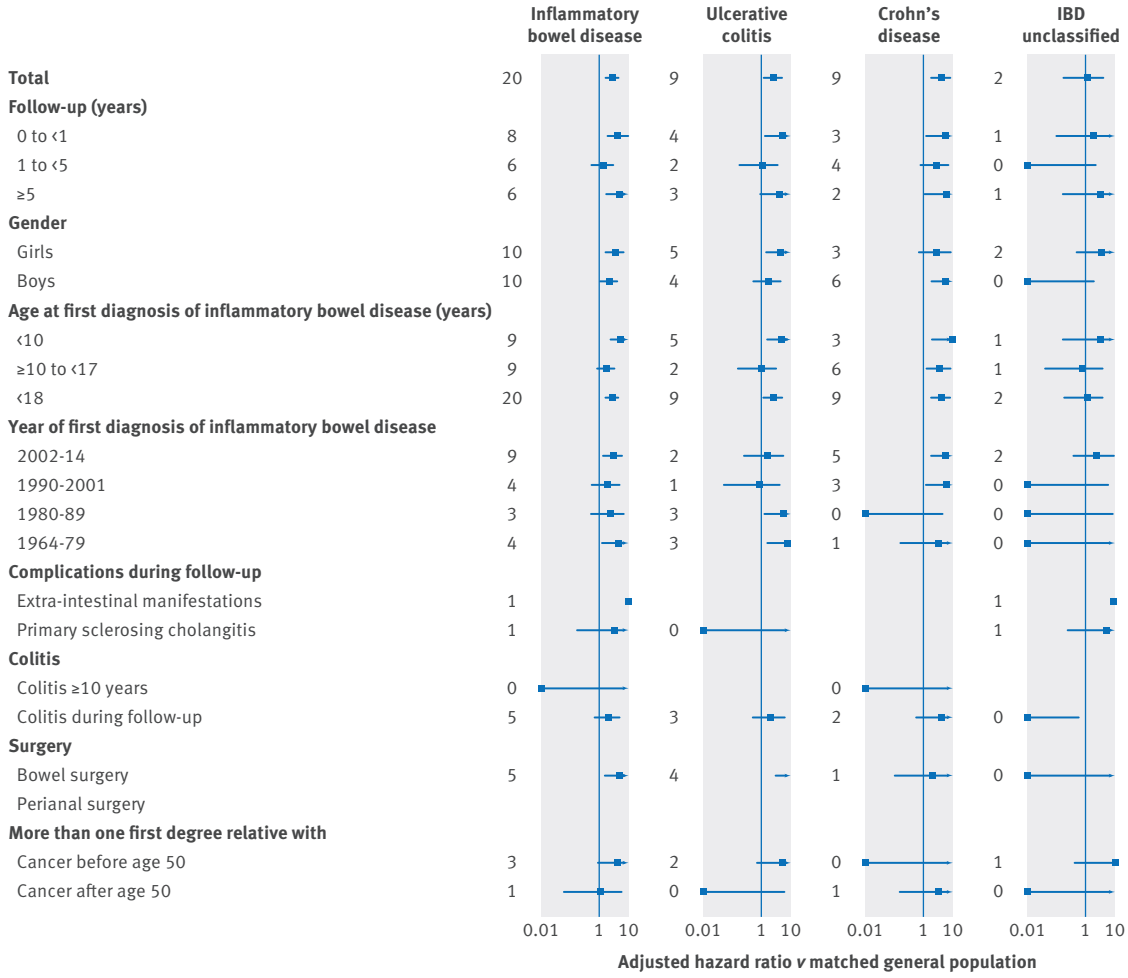

Fig 5 | Adjusted* hazard ratios for all cancer occurring before the 18th birthday in patients with childhood onset (<18 years) inflammatory bowel disease and matched general population comparators 1964-2014 (first year of follow-up included). Numbers next to the forest plot represent the number of cancers 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).[27] 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.[45] 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,[6 21] 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,[46] 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.[47] A more recent US case-control study reported an odds ratio of 12 for small bowel adenocarcinoma in patients with Crohn's disease.[48] 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.[46-48]

We also examined the risk of lymphoid neoplasms in childhood onset inflammatory bowel disease. A previous US study[26] 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.[49] 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).[50] 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.[17] 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[5152] and that relative risks have decreased over time.[621] 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%.[34] 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[53] and many cancers.[54] 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.

Contributor and sources: OO, JFL, JA, PF conceived and designed study. OO was responsible for acquisition of data. MCS, PF, and OO analysed the data. JFL and OO drafted the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content and approval of final version. OO is the guarantor.

Funding: OO was supported by grants from the Swedish Medical Society (project grants, the fund for research in gastroenterology and the Ihre Foundation), Mag-tarmfonden, the Jane and Dan Olsson Foundation, the Mjölkdroppen Foundation, The Bengt Ihre Research Fellowship in gastroenterology and Karolinska Institutet Foundations while working on this project. Financial support was also provided through the regional agreement on medical training and clinical research between Stockholm County Council and the Karolinska Institutet (ALF), the Swedish Cancer Society, the Swedish Research Council, and the Swedish Foundation for Strategic Research. None of the funding organisations had any role in the design and conduct of the study; in the collection, management, and analysis of the data; or in the preparation, review, and approval of the manuscript.

Competing interests: All authors have completed the Unified Competing Interest form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the Ethics Review Board in Stockholm (2007/785-31/5; 2011/1509-32; 2015/0004-31).

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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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