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Cancer Incidence in Patients with Ulcerative Colitis Naïve to or Treated with Thiopurine and Targeted Therapies– a cohort study 2007 to 2022 with comparison to the general population

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Statement of Interests

Authors' declaration of personal interests

JF Ludvigsson has coordinated an unrelated study on behalf of the Swedish IBD Quality Register (SWIBREG). That study received funding from Jansen Corporation. Ludvigsson has also received financial support from MSD for developing a paper reviewing national healthcare registers in China. Ludvigsson has an ongoing research collaboration with Takeda about celiac disease.

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J Halfvarson has served as speaker and/or advisory board member for AbbVie, Alfasigma, Bristol Myers Squibb, Celgene, Celltrion, Eli Lilly, Dr. Falk Pharma and the Falk Foundation, Ferring, Galapagos, Gilead, Hospira, Index Pharma, Janssen, MEDA, Medivir, Medtronic, Merck, MSD, Olink Proteomics, Novartis, Pfizer, Prometheus Laboratories, Sandoz, Shire, Takeda, Thermo Fisher Scientific, Tillotts Pharma, Vifor Pharma, UCB, and has received grant support from Janssen, MSD, and Takeda.

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J Eriksson reports participation in research projects funded by pharmaceutical companies, all regulator-mandated phase 4 studies, all with funds paid to the institution where she is employed (no personal fees) and with no relation to the work reported in this manuscript

HT Sørensen reports that the Department of Clinical Epidemiology, Aarhus University, receives funding for other studies from companies in the form of institutional research grants to (and administered by) Aarhus University with no relation to this manuscript.

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Final approval: All authors

Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All authors

Availability of data

The data analysed for this article cannot be shared publicly, because of Swedish legislation.

Ethical permission

The study was approved by the Regional Ethics Committee in Stockholm (Dnr - 2021-06209-01, 2022-04384-02, and 2023-04868-02). Individual informed consent was not required for this entirely register-based study.

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Abstract

Background: Cancer incidence data including absolute risk differences are needed for clinical risk communication to patients receiving modern-day treatments for ulcerative colitis (UC).

Methods: We linked nationwide Swedish health registers and assessed incident cancers in patients with UC in 2007-2022. We computed age-stratified incidence rates (IRs), IR differences and hazard ratios (HRs) in a naïve cohort with no immunomodulatory treatment, and in cohorts treated with thiopurine or targeted therapies. General population comparator subjects were matched (by age, sex, calendar year, and area of residence) to each treatment cohort. We used a once-exposed – always exposed design.

Results: We identified 63,925 patients with UC in partly overlapping cohorts and 593,072 comparators with a total follow-up time of 5,800,089 years (median 8.1 years).

The IRs were elevated compared to the general population in naïve patients: 2.7 extra cancer cases per 1000 person years (HR:1.12, 95%CI:1.09-1.16), in thiopurine-treated patients: 3.4 extra cases (HR:1·48;1.37-1.61), TNFi-treated: 2.7 extra cases (HR:1·41;1.24-1.62), Thiopurine+TNFi-treated: 2.42 extra cases (HR:1.44;1.19-1.75), vedolizumab-treated: 2.88 extra cases (HR:1.27;0.90-1.79). The IR differences were not significantly increased in patients treated with ustekinumab 0.57 (HR:0.87;0,39-1.93) and tofacitinib -0.69 (HR:0.84;0.25-2.77). Across all treatment groups, the IR differences compared to the general population were highest in patients ≥60 years. The differences were driven by colorectal cancer, hepatobiliary cancer, lymphoma, and basal cell skin carcinoma.

Conclusion: Elevated cancer incidence was observed in patients with UC amounting to around 3 extra cases of cancer per 1000 years. Cancer risks varied more among groups defined by age than by treatment.

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Keywords: inflammatory bowel disease; ulcerative colitis; thiopurine; tumour necrosis factor inhibitor; vedolizumab; ustekinumab; tofacitinib; cancer; incidence; population-based

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Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) characterized by chronic inflammation of the colon and rectum, due to an abnormal immune response to environmental factors among genetically susceptible individuals.[1] Medical therapies such as thiopurines, tumour necrosis factor inhibitors (TNFi), and other targeted therapies (TT) which decrease inflammation, are used as medical treatment of UC, and should preferably be administered early in the disease course to avoid irreversible tissue damage[2].

Cancers in patients with UC can arise through several mechanisms: they can be sporadic and unrelated to the disease, they can share risk factors with UC, be caused by the disease, e.g., through chronic inflammation, or be causally linked with the treatment itself [3, 4]. At the same time, improved disease control via effective treatment might prevent or reduce a disease-mediated increased risk. Studies have demonstrated that, across all treatment types, certain gastrointestinal cancers, such as colorectal cancer (CRC)[5-8] and hepatobiliary cancer [9, 10] are more common in patients with UC than in the population. Patients with UC are also at elevated risk of extraintestinal cancers[11].

Investigations of the association between cancer and UC medication have focused primarily on thiopurines[12-18]. In meta-analyses of studies comparing patients with IBD with various treatment exposures, thiopurines have been associated with diminished risk of CRC[13, 14, 19], but elevated risks of skin cancer [17, 18] and lymphoma[16, 20]. To date, meta-analyses based on non-experimental[12, 21-26], and

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placebo-controlled trials[27], have not linked TNFi use in IBD to increased risk of overall cancer risk [21, 22, 27], lymphoma [23], melanoma [24, 25], or cervical cancer [26], except for one study, indicating a slightly greater risk of lymphoma in TNFi users than non-users [20]. Newer targeted therapies have mainly been evaluated within randomized controlled studies with short follow-up time [28, 29] (**Table S1**).

For clinical risk communication and decision making, HR is a difficult metric because it conveys the relative change without specifying the absolute risk. In this study, the aim was to provide an overview of the absolute and excess occurrence of cancer in patients with UC with or without exposure to specific UC drugs vs the cancer incidence in the general population with the same age/sex composition.

Methods

Study design

Nationwide cohort study based on national health registers with prospectively captured data from routine medical practice.

Setting

Health care in Sweden is tax-funded. All citizens have equal access to care. The unique personal identity number assigned to all residents allows for linkage of data in nationwide registers containing information on vital status, emigration, morbidity, mortality, and histopathology, with complete follow-up.[30] In Sweden, treatment with thiopurines, primarily azathioprine, was initiated during the early/mid

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1980s. Infliximab, the first TNFi, was approved for the treatment of UC in 2006, adalimumab in 2012, and golimumab in 2013. Vedolizumab (the first Integrin inhibitor) was approved in 2014, tofacitinib (the first Janus kinase inhibitor) in 2018, and ustekinumab (an Interleukin inhibitor) in 2019 (**Figure S1**).

Data sources

Baseline and follow-up data, including patient demographics, disease characteristics, treatments, and outcomes were obtained from diagnostic listings in the National Quality Register SWIBREG,[31] the Swedish National Patient Register,[32] the Prescribed Drug Register,[33, 34] the Swedish Cancer Register,[35] and the Total Population Register (**Table S2**).[36]

Participants

We identified all Swedish patients with UC. Patients with incident UC were included from Jan 1, 2007 to December 31, 2021 if they had ≥2 first-ever listings of diagnostic codes of UC in non-primary outpatient clinic or inpatient care. Patients with prevalent UC were identified as those with ≥2 listings of UC before July 1, 2008 and - in case of different IBD subtype diagnoses - the last 2 diagnostic listings (before July 1, 2008) indicating UC.[37, 38] Each patient was matched by age, sex, and place of residence with up to 10 general population comparator subjects who were free of IBD on the date of the first UC diagnosis of the matched case (diagnostic codes provided in **Table S3**). Exclusion criteria at baseline for all participants were: (1) absolute or relative contraindication to thiopurine and/or TNFi (*i.e.*, human immunodeficiency virus, HIV, chronic hepatitis or other advanced liver disease, solid organ or bone marrow transplantation,

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or advanced kidney disease), or (2) previous use of immunomodulators (i.e., azathioprine, mercaptopurine or methotrexate), TNFi, or other targeted therapies (i.e., vedolizumab, ustekinumab or tofacitinib) before the UC diagnosis/match date (**Table S4**). Participants with any previous invasive cancer were excluded from the analyses of any cancer. For cancer subtype-specific outcomes, participants were only excluded if they had a history of the same outcome/cancer type as that under study.

Exposure

The exposures of interest were: *thiopurine, TNFi* (infliximab, adalumumab, or golimumab), *thiopurine+TNFi*, i.e., combined treatment with thiopurine and TNFi, *vedolizumab*, *ustekinumab*, and *tofaniticib* (**Table S5**). To avoid detection and surveillance bias around UC diagnosis and follow-up, we employed a 1-year latency period between the exposure (date of UC diagnosis/initiation of the treatment under study) and outcome assessment (cancer diagnosis).

The outcomes were assessed in seven treatment cohorts. Patients were considered exposed to a medication from 1 year after its initiation until the end of follow-up. For all participants, follow-up ended with an outcome event, death, emigration, or December 31, 2022 whichever occurred first. The start and end of follow-up in the treatment cohorts were:

naïve, follow-up started 1 year after UC diagnosis in incident patients and from one year after July 1, 2008 in patients with prevalent UC, and, in addition to end of follow-up, as described above, naïve patients were censored 1 year after start of treatment with thiopurine, TNFi, vedolizumab, ustekinumab, or tofacitinib. For the drug exposures thiopurine, TNFi, vedolizumab, ustekinumab, and tofaniticib,

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patients were followed from 1 year after first prescription redemption/treatment registration to end of follow-up. For *thiopurine+TNFi* patients were considered exposed from 1 year after first combined treatment episode (defined as at least 3 months' overlapping exposure) to the end of follow-up. Patients could thus contribute person-time to multiple treatment groups and one cancer event could be assigned to multiple treatment groups. All statistical comparisons were performed vs matched general population comparators.

Outcome

Incident cancers were identified in the Cancer Register through ICD codes and the histopathological 3-digit code (C24), used since 1958. Diagnostic coding of the different cancer types is listed in **Table S6.**

We assessed incident cancers according to organ site, reported as:

- *Cancers associated with UC*: CRC, small bowel, pancreatic, and hepatobiliary cancer.
- *Cancers with known or suspected association with thiopurine or TNFi:* malignant melanoma, basal cell skin carcinoma, squamous cell carcinoma of the skin, lymphoma, other haematological malignancy, cervical cancer, and urinary tract cancer.[11]
- *Other common cancer forms:* breast cancer, prostate cancer, lung cancer, uterine cancer, and brain or spinal cord cancers.

Covariates

Diagnostic listings during 5 years preceding the UC match date were used to characterize all study participants in terms of comorbid conditions (**Table S7)** and medication use (**Table S8**)

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occurring/dispensed before the matching date.[34] Patients with UC were further characterized by surgery (colectomy or other bowel surgery, **Table S9**),[39] and presence of primary sclerosing cholangitis (PSC).

Statistical methods

Baseline characteristics are presented as number and proportion (%) for categorical variables, or as mean and standard deviation (SD) or median and interquartile range (IQR), for continuous variables. The cumulative incidences and incidence rates (IRs) (number of events/1000 person years) of any cancer and cancer type are presented for each cohort, as well as standardized to the age- and sex-distribution of the Swedish population in 2023. The cumulative incidence of any cancer is presented stratified by age at start of follow-up (<18, 18- <40y, 40- <60, ≥60 years). Differences between patient cohorts and matched population comparators are presented as IR differences and adjusted (age, sex, region, calendar year) hazard ratios (HRs) from Cox regression models with 95% confidence intervals (CI) overall and stratified by age at exposure start. The proportional hazard assumption was tested by inclusion of an interaction term of exposure and the time scale (follow-up time). Only patients with at least one available population comparator subject were included for each outcome.

All statistical tests were two-sided and $p < 0.05$ was considered statistically significant. Data were analysed in SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA).

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Results

We identified 40,778 patients with incident UC 2007-2021 and 32,423 patients with prevalent UC as of July 1, 2008. After exclusion of participants with previous use of immunomodulators or targeted therapies, or contraindication to their use, 63,925 patients remained. The total number of matched population comparator subjects was 593,072 (**Table S10**).

Characteristics of the study population

Patient characteristics differed among treatment cohorts (**Table 1**). Patients in the thiopurine+TNFi cohort were the youngest at diagnosis/match (median age 26.7 years) and at start of follow-up (median age 32.2) and had fewer comorbidities. Patients treated with vedolizumab, ustekinumab, and tofacitinib had the largest proportion of extensive disease (67-72%). Patients in the naïve cohort were oldest (median age at start of follow-up = 46.6 years), more often had comorbidities, and less often extensive disease (31%).

Characteristics for patients with incident and prevalent UC are presented separately in **Table S11**, and detailed characteristics of the treatment cohorts and the number and proportion of patients excluded because of previous cancer are listed in **Table S12a-b.**

Patients starting in the naïve cohort largely remained within that cohort (86%). Approximately one fourth (23%) the patients starting in the thiopurine cohort were later followed in the thiopurine+TNFi cohort, and 36% of patients starting in the TNFi cohort were later followed in the thiopurine+TNFi

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cohort (**Figure S2**). The median follow-up was 11.7 years in the naïve cohort, 6.99 years in the thiopurine, 4.3 years in the TNFi, and 5.1 years in the thiopurine+TNFi , 2.8 in the Vedolizumab, 1.6 years in the Ustekinumab, and 1.7 years in the Tofaniticib cohort (**Table S13a** and **b**).

Cumulative cancer incidence

During a total follow-up of 5,800,089 person years, 52,759 cancer events in 656,997 (63,925+593,072) participants were registered in the seven partly overlapping treatment cohorts. The cumulative 5-year incidence of any cancer (for all age-groups combined) was 5.3% in the naïve cohort vs 4·1% in its matched general population comparator group, 4.3% in the thiopurine cohort (vs 2.5%), 3.6% in TNFi cohort (vs 2.1%), 3.4% in thiopurine+TNFi cohorts (vs 1.9%), 3.9% in the Vedolizumab cohort (vs 2.6%), 1.4% in the Ustekinumab cohort (vs 2.4%), and 1.0% in the Tofaniticib cohort (vs 2.7%), **Table S13a** and **b.** When stratifying by age groups, the cumulative incidence of any cancer was highest for patients with UC ≥60 years and their population comparators, and lowest for participants < 18 years (**Figure 1**).

Incidence rate differences and hazard ratios for cancer overall

The IR difference versus the population for any cancer was 2.66 cases/1000 person years in the naïve cohort, 3.38 in the thiopurine, 2.69 in the TNFi, 2.42 in the thiopurine+TNFi cohort, and 2.88 in the vedolizumab cohort, with overlapping CIs. The cohorts treated with ustekinumab and tofaniticib had few cancer events and large CIs that were not significantly increased (**Figure 2**).

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The IR differences were not significantly elevated in paediatric patients (age <18 years), while the IR differences for adult patients were more pronounced, especially for middle-aged (40 to <60) and elderly (≥60 years) patients, e.g., 1.76 to 1.57 cases/1000 years in the naïve cohort, and 3.45 to 9.69 cases/1000 years in the thiopurine cohort. The contrary was observed for the HRs which were increased in younger patients (18 to <40 years) are rarely in patients ≥60 years.

Incidence rate differences and hazard ratios by cancer type

The IR differences were elevated in the naive cohort and in cohorts treated with TNFi and/or thiopurine for CRC, hepatobiliary cancer and lymphoma, although lower estimates were observed in the naïve group for CRC and lymphoma (**Figure 3, Table S14a**). The IR difference for CRC was between 0·12 cases/1000 years in the naïve group and 0.52 to 0.71 cases in patients treated with thiopurines and/or TNFi. The IR difference was 0·32 to 0·45 cases/1000 years for hepatobiliary cancer, 0.08 to 0.61 cases/1000 years for lymphoma, and 0.77 to 1.62 cases/1000 years for basal cell carcinoma. In the cohorts treated with vedolizumab, ustekinumab, and tofacitinib events were few for each cancer type (**Figure S3, Table S14b**). We observed no significantly increased IRs for common cancer types such as breast, lung, and uterine cancer in any of the treatment cohorts.

The highest HRs compared to the general population were found for hepatobiliary cancer: naïve 3.47; thiopurine 5.43; TNFi 5.95; thiopurine+TNFi 5.02 (**Figure 4**). When stratifying patients by presence of PSC, the IR differences were more similar between treatment cohorts: PSC naïve cohort 6.26 extra cases; Non-PSC naive cohort 0.28 extra cases (**Table S15**).

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For CRC, the HR was not significantly elevated in the naïve cohort, but in the cohorts treated with thiopurine and/or TNFi (ranging from 2·10 to 3.03). Basal cell carcinoma HRs were elevated in the treatment naive (1.21) and in cohorts treated with thiopurine and/or TFi (1.48 to 1.79). The HR for lymphoma was elevated in the thiopurine cohort (1.64), TNFi (2.78), and thiopurine+TNFi (6.28), but not in the naïve cohort. No elevated HRs were observed for malignant melanoma, urinary tract cancer, cervical cancer, breast, uterine, prostate, lung, or brain or spinal cord cancers in UC patients vs. the general population cohort, regardless of treatment exposure. HRs for patients treated with vedolizumab, ustekinumab, and tofacitinib are in **Figure S4**.

Discussion

In this cohort study including more than 60,000 patients with UC followed for a median of 8.1 years, we observed elevated cancer incidences compared to the general population in patients treated with thiopurine (3.38 additional cases/1000 patients and year), TNFi (2.69 additional cases), thiopurines+TNFi (2.42 additional cases), and vedolizumab (2.88 additional cases). The IRs differences were not increased in cohorts treated with ustekinumab and tofacitinib but included fewer patients. Importantly, patients naïve to immunomodulatory drugs also had an elevated cancer incidence in the order of 2.66 additional cases/1000 years. As expected, we observed large differences across age strata, with the highest increase in absolute risk among middle-aged and elderly patients. Finally, we observed elevated incidences for CRC, hepatobiliary cancer, lymphoma, and basal cell carcinoma, but no risk increases for other common cancer types in any of the treatment cohorts.

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A recent Danish study reported increased risk of cancer in patients with IBD following thiopurine use with or without TNFi[40]. The study reported an adjusted HR of 1.59 for cancer in patients with IBD < 50 years of age vs reference population, which aligns well with our results of HR 1.54 in naïve patients 18 to <40 years. The Danish study did not report absolute risk estimates in relation to the population, but focused on HRs, which were were adjusted for several factors, including socio-economic status and disease severity, thus reflecting the relative risk increase from IBD and IBD medication.

Cancers associated with UC

We observed elevated incidences of certain gastrointestinal cancer types associated with UC, *e.g.,* CRC and hepatobiliary cancer. In clinical practice, treatment choices often follow a step-up approach guided by the severity of inflammation, and chronic inflammation is an important driver of cancer risk. Patients requiring thiopurine and/or TNFi treatment (likely due to extensive and more active disease) had a higher incidence of CRC (0.71 additional case of CRC per 1000 person years in patients needing combined treatment with thiopurine and TNFi) than IBD-free individuals of the same age and sex in the general population cohort. A meta-analysis investigating risk factors and protective factors for the CRC development in patients with IBD has reported a pooled odds ratio of 0·55 (95%CI, 0.37-0.82) for thiopurine use (according to 19 studies), and an OR of 0.71 (95%CI, 0.14-3.67) for TNFi use (according to 4 studies),[19] suggesting protective effects of these medications.

We observed elevated IR differences and HRs for hepatobiliary cancer versus the matched population comparators, although its cumulative incidence was low (0.5% after a median 11.7 years of follow-up), compared to several other cancer types. A meta-analysis based on seven studies reported an incidence rate ratio of 2.05 (95%CI 1.52- 2.76) for hepatobiliary cancer in patients with UC compared to the

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general population.[11]. PSC has been identified as a risk factor for death from hepatocellular carcinoma and cholangiocarcinoma [10], but with no excess risk reported from thiopurine of TNFi exposure[41]. In our study, the prevalence of PSC was lower in the naïve cohort (3·8% at end of follow-up) than in cohorts treated with thiopurine and/or targeted therapies (4.4 to 6.4%) and the hazard ratios for hepatobiliary cancer were similar between the treatment cohorts when stratifying for presence of PCS.

IBD has been reported to be associated with small bowel cancer [42], but these are rare, and in the present study no cancer events occurred in the TNFi and thiopurine+TNFi cohorts. Although pancreatic cancer has been found to be slightly more prevalent in patients with than without IBD[43] , it has not been associated with immunomodulators or targeted therapies.

Extraintestinal cancers

A previous meta-analysis reported an incidence rate ratio of 1.15 [95% confidence interval (CI): 1·02-1·31] for extraintestinal cancers overall in UC patients (irrespective of UC medication status) compared to the general population.[11]. We observed increased incidences of basal cell carcinoma, squamous cell carcinoma, and lymphoma. Lymphoma incidence was increased only in the groups treated with thiopurine and/or TNFi, which is in line with previous reports.[44 20 45] The findings of increased incidence of basal cell carcinoma across all treatment groups also aligns with previous reports. [46]

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Strengths and limitations

This study was enabled by the availability of prospectively recorded data from registers providing virtually complete follow-up for routine medical practice. Because of the population-based setting, our results should be highly generalizable to similar populations. Previous studies have assessed cancer diagnoses according to organ site by using diagnostic codes. To enhance the specificity of a cancer diagnosis, we also required histopathologic confirmation from the Cancer Register. The 1-year lag time decreased detection bias, because cancer events during the first year following UC diagnosis were not considered events.

The study has several limitations. In studying cancer as an outcome, long follow-up is preferable. However, to ensure that all included patients were new users, *i.e.*, naïve to thiopurine /TNFi therapy, we did not include prevalent patients earlier than 3 years after the start of the Prescribed Drug Register. Our median follow-up was 8 years, and we know from previous research that colorectal cancer risk increases after 8-10 years after diagnosis. Our results must therefore be interpreted considering limited follow-up time. In addition, follow-up time was even shorter for the patients receiving the newer targeted therapies tofacitinb (7.3 years), and vedolizumab (6.2 years). The newer targeted therapies were approved 2014-2019, i.e., during a time when treatment has become more proactive, individualized, and when cancer surveillance has intensified.

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We were able to present estimates of cancer risk among treatment-naïve patients as a comparison group, but this study was not designed to compare the treatment groups. The age and sex distributions in each of the treatment cohorts vs the general population cohorts were controlled through the matching, but pronounced differences existed in, e.g., age and disease severity between the different treatment groups, thus precluding comparison of incidence across treatment groups. We used a once exposed-always exposed approach and did not consider actual exposure time.

Clinical implications

The aim of this study was to provide an overview of cancer risk among patients treated with modern IBD medications. Our design answered the following question: What is the absolute risk cancer in patients with IBD requiring immunomodulatory treatment, and the relative risk with respect to individuals without IBD and associated treatment? The question whether advanced treatments differ with regards to cancer risk after careful adjustment for relevant confounders is another question, that we did not address herein.

CRC surveillance programs are an established component of health care for patients with IBD.[47] In the general population in Sweden the program Screening of Swedish colons (SCREESCO), targeting individuals aged 59-62 years, was initiated in 2014. Screening of patients with IBD for other forms of cancer, such as hepatobiliary cancer and basal cell skin carcinoma, has been suggested. For non-

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melanoma skin cancer, Sweden has no national screening recommendations, and the overall absolute risks were low. Therefore, evidence remains insufficient to support specific surveillance strategies. Reassuringly, elevated risks were not observed for common cancers such as breast, prostate, and lung cancer, regardless of treatment status.

Conclusion

Comparing UC to the general population, the additional risk of developing cancer amounts to 2 to 3 extra cases of cancer per 1000 years, also in patients naïve to immunomodulatory drugs. This additional risk displayed large variations with age but – once age and sex were considered - relatively small differences between different UC therapies.

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Figure legends

Figure 1. Time to any cancer in up in cohorts of patients with UC, stratified by age (<18y, 18 - <40y, 40 - <60y, ≥60y) and treatment at start of follow-up: Naïve (no treatment with thiopurine, tumor necrosis factor inhibitors (TNFi) and other targeted therapies), thiopurine (treatment with thiopurines), TNFi (treatment with TNFi), thiopurine+TNFi (overlapping treatment with thiopurines and TNFi), treatment with vedolizumab, ustekinumab, and tofacitinib

Figure 2. Incidence rate (IR) differences (cases/1000 person years) and hazard ratios with 95% confidence intervals (Cis) of any cancer in cohorts of patients with ulcerative colitis versus matched general population comparators, stratified by age (<18, 18 - <40, 40 - <60, ≥60 years) and treatment at start of follow-up: naive (no treatment with thiopurine, tumor necrosis factor inhibitors (TNFi) and other targeted therapies), thiopurines (treatment with thiopurines), TNFi (treatment with TNFi), thiopurine+TNFi (overlapping treatment with thiopurines and TNFi), and treatment with vedolizumab, ustekinumab, and tofacitinib

Figure 3. Incidence rate (IR) differences (cases/1000 person years) with 95% confidence intervals (Cis) for UC-associated cancers, cancers with known/suspected association with thiopurine or TNFi treatment, and cancers common in the population in cohorts of patients with UC *vs* matched general population comparators, stratified by age (<18, 18 to <40, 40 to <60, and ≥60 years) and treatment at start of follow-up: naïve (no past or ongoing treatment with thiopurines, tumour necrosis factor inhibitors (TNFi) or other targeted therapies); thiopurines; TNFi; and thiopurines+TNFi (overlapping treatment with thiopurines and TNFi)

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Figure 4. Hazard ratios with 95% confidence intervals (CIs) for UC-associated cancers, cancers with known/suspected association with immunomodulatory treatment, and cancers common in the population, in cohorts of patients with UC *vs* matched general population comparators, stratified by age (<18, 18 to <40, 40 to <60, and ≥60 years) and treatment at the start of follow-up: naïve (no past or ongoing treatment with thiopurines, tumour necrosis factor inhibitors (TNFi) or other targeted therapies); thiopurines; TNFi; and thiopurines+TNFi (overlapping treatment with thiopurines and TNFi)

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REFERENCES

1. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. (1474-547X (Electronic)).
2. Shah SC, Colombel JF, Sands BE, Narula N. Mucosal Healing Is Associated With Improved Long-term Outcomes of Patients With Ulcerative Colitis: A Systematic Review and Meta-analysis. (1542-7714 (Electronic)).
3. Axelrad JE, Lichtiger S, Yajnik V. Inflammatory bowel disease and cancer: The role of inflammation, immunosuppression, and cancer treatment. World journal of gastroenterology. 2016;22(20):4794-801.
4. Kimmel JA-O, Axelrad JA-O. The Complex Interplay Between Inflammatory Bowel Disease and Malignancy. (1534-312X (Electronic)).
5. Wang Y, Wang P, Shao L. Correlation of ulcerative colitis and colorectal cancer: a systematic review and meta-analysis. J Gastrointest Oncol. 2021;12(6):2814-22.
6. Olen O, Erichsen R, Sachs MC, Pedersen L, Halfvarson J, Askling J, et al. Colorectal cancer in ulcerative colitis: a Scandinavian population-based cohort study. Lancet. 2020;395(10218):123-31.
7. Everhov Å HA-O, Erichsen R, Järås J, Pedersen L, Halfvarson JA-O, Askling J, et al. Colorectal cancer in elderly-onset inflammatory bowel disease: A 1969-2017 Scandinavian register-based cohort study. LID - 10.1111/apt.17175 [doi]. (1365-2036 (Electronic)).
8. Everhov AH, Ludvigsson JF, Jaras J, Erichsen R, Pedersen L, Halfvarson J, et al. Colorectal Cancer in Childhood-onset Inflammatory Bowel Disease: A Scandinavian Register-based Cohort Study, 1969-2017. Journal of pediatric gastroenterology and nutrition. 2022;75(4):480-4.
9. Huang J, Li X, Hong J, Huang L, Jiang Q, Guo S, et al. Inflammatory bowel disease increases the risk of hepatobiliary pancreatic cancer: A two-sample Mendelian randomization analysis of European and East Asian populations. Cancer Med. 2023;12(12):13599-609.
10. Erichsen R, Olen O, Sachs MC, Pedersen L, Halfvarson J, Askling J, et al. Hepatobiliary Cancer Risk in Patients with Inflammatory Bowel Disease: A Scandinavian Population-Based Cohort Study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2021;30(5):886-94.
11. Lo B, Zhao M, Vind I, Burisch J. The Risk of Extraintestinal Cancer in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis of Population-based Cohort Studies. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2021;19(6):1117-38 e19.
12. Elmahdi R, Lemser CE, Thomsen SB, Allin KH, Agrawal M, Jess T. Development of Cancer Among Patients With Pediatric-Onset Inflammatory Bowel Disease: A Meta-analysis of Population-Based Studies. (2574-3805 (Electronic)).
13. Zhu Z, Mei Z, Guo Y, Wang G, Wu T, Cui X, et al. Reduced Risk of Inflammatory Bowel Disease-associated Colorectal Neoplasia with Use of Thiopurines: a Systematic Review and Meta-analysis. Journal of Crohn's & colitis. 2018;12(5):546-58.

14. Lu MJ, Qiu XY, Mao XQ, Li XT, Zhang HJ. Systematic review with meta-analysis: thiopurines decrease the risk of colorectal neoplasia in patients with inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2018;47(3):318-31.
15. Jess T, Lopez A, Andersson M, Beaugerie L, Peyrin-Biroulet L. Thiopurines and risk of colorectal neoplasia in patients with inflammatory bowel disease: a meta-analysis. (1542-7714 (Electronic)).
16. Kotlyar DS, Lewis JD, Beaugerie L, Tierney A, Brensinger CM, Gisbert JP, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. (1542-7714 (Electronic)).
17. Huang SZ, Liu ZC, Liao WX, Wei JX, Huang XW, Yang C, et al. Risk of skin cancers in thiopurines-treated and thiopurines-untreated patients with inflammatory bowel disease: A systematic review and meta-analysis. Journal of gastroenterology and hepatology. 2019;34(3):507-16.
18. Ariyaratnam J, Subramanian V. Association between thiopurine use and nonmelanoma skin cancers in patients with inflammatory bowel disease: a meta-analysis. (1572-0241 (Electronic)).
19. Wijnands AM, de Jong ME, Lutgens M, Hoentjen F, Elias SG, Oldenburg B, et al. Prognostic Factors for Advanced Colorectal Neoplasia in Inflammatory Bowel Disease: Systematic Review and Meta-analysis. Gastroenterology. 2021;160(5):1584-98.
20. Chupin A, Perduca V, Meyer A, Bellanger C, Carbonnel F, Dong C. Systematic review with meta-analysis: comparative risk of lymphoma with anti-tumour necrosis factor agents and/or thiopurines in patients with inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2020;52(8):1289-97.
21. Piovani DA-O, Danese SA-O, Peyrin-Biroulet LA-O, Nikolopoulos GA-O, Bonovas SA-O. Systematic review with meta-analysis: biologics and risk of infection or cancer in elderly patients with inflammatory bowel disease. (1365-2036 (Electronic)).
22. Borren NZ, Ananthakrishnan AN. Safety of Biologic Therapy in Older Patients With Immune-Mediated Diseases: A Systematic Review and Meta-analysis. (1542-7714 (Electronic)).
23. Yang C, Huang J, Huang X, Huang S, Cheng J, Liao W, et al. Risk of Lymphoma in Patients With Inflammatory Bowel Disease Treated With Anti-tumour Necrosis Factor Alpha Agents: A Systematic Review and Meta-analysis. (1876-4479 (Electronic)).
24. Singh S, Nagpal SJ, Murad MH, Yadav S, Kane SV, Pardi DS, et al. Inflammatory bowel disease is associated with an increased risk of melanoma: a systematic review and meta-analysis. (1542-7714 (Electronic)).
25. Esse S, Mason KJ, Green AC, Warren RB. Melanoma Risk in Patients Treated With Biologic Therapy for Common Inflammatory Diseases: A Systematic Review and Meta-analysis. (2168-6084 (Electronic)).
26. Mann SA-O, Jess T, Allin K, Elmahdi R. Risk of Cervical Cancer in Inflammatory Bowel Disease: A Meta-Analysis of Population-Based Studies. (2155-384X (Electronic)).
27. Williams CJ, Peyrin-Biroulet L, Ford AC. Systematic review with meta-analysis: malignancies with anti-tumour necrosis factor-alpha therapy in inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2014;39(5):447-58.
28. Bezzio C, Vernero MA-O, Ribaldone DA-O, Alimenti E, Manes G, Saibeni SA-O. Cancer Risk in Patients Treated with the JAK Inhibitor Tofacitinib: Systematic Review and Meta-Analysis. LID - 10.3390/cancers15082197 [doi] LID - 2197. (2072-6694 (Print)).

29. Russell MD, Stovin C, Alveyn E, Adeyemi O, Chan CKD, Patel V, et al. JAK inhibitors and the risk of malignancy: a meta-analysis across disease indications. Annals of the rheumatic diseases. 2023;82(8):1059-67.
30. Laugesen K, Ludvigsson JF, Schmidt M, Gissler M, Valdimarsdottir UA, Lunde A, et al. Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. Clinical epidemiology. 2021;13(1179-1349 (Print)):533-54.
31. Ludvigsson JF, Andersson M, Bengtsson J, Eberhardson M, Fagerberg UL, Grip O, et al. Swedish Inflammatory Bowel Disease Register (SWIBREG) - a nationwide quality register. Scandinavian journal of gastroenterology. 2019;54(9):1089-101.
32. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC public health. 2011;11:450.
33. Wallerstedt SM, Wettermark B, Hoffmann M. The First Decade with the Swedish Prescribed Drug Register - A Systematic Review of the Output in the Scientific Literature. Basic & clinical pharmacology & toxicology. 2016;119(5):464-9.
34. Broms G, Soderling J, Sachs MC, Halfvarson J, group Ss, Myrelid P, et al. Capturing biologic treatment for IBD in the Swedish Prescribed Drug Register and the Swedish National Patient Register - a validation study. Scandinavian journal of gastroenterology. 2021;56(4):410-21.
35. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta oncologica (Stockholm, Sweden). 2009;48(1):27-33.
36. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaelsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. European journal of epidemiology. 2016;31(2):125-36.
37. Everhov AH, Sachs MC, Malmborg P, Nordenvall C, Myrelid P, Khalili H, et al. Changes in inflammatory bowel disease subtype during follow-up and over time in 44,302 patients. Scandinavian journal of gastroenterology. 2019;54(1):55-63.
38. Jakobsson GL, Sternegard E, Olen O, Myrelid P, Ljung R, Strid H, et al. Validating inflammatory bowel disease (IBD) in the Swedish National Patient Register and the Swedish Quality Register for IBD (SWIBREG). Scandinavian journal of gastroenterology. 2017;52(2):216-21.
39. Forss A, Myrelid P, Olen O, Everhov AH, Nordenvall C, Halfvarson J, et al. Validating surgical procedure codes for inflammatory bowel disease in the Swedish National Patient Register. BMC medical informatics and decision making. 2019;19(1):217.
40. Wewer MD, Letnar G, Andersen KK, Malham M, Wewer V, Seidelin JB, et al. Thiopurines and the Risk of Cancer in Patients With Inflammatory Bowel Disease and Reference Individuals Without Inflammatory Bowel Disease - A Danish Nationwide Cohort Study (1996-2018). LID - S1542-3565(24)00772-9 [pii] LID - 10.1016/j.cgh.2024.08.006 [doi]. (1542-7714 (Electronic)).
41. Biron A, Beaugerie L, Chazouilleres O, Kirchgesner J. Impact of thiopurines and tumour necrosis factor antagonists on primary sclerosing cholangitis outcomes in patients with inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2022;56(5):857-68.
42. Axelrad JE, Olen O, Sachs MC, Erichsen R, Pedersen L, Halfvarson J, et al. Inflammatory bowel disease and risk of small bowel cancer: a binational population-based cohort study from Denmark and Sweden. Gut. 2021;70(2):297-308.

43. Everhov AH, Erichsen R, Sachs MC, Pedersen L, Halfvarson J, Askling J, et al. Inflammatory bowel disease and pancreatic cancer: a Scandinavian register-based cohort study 1969-2017. Alimentary pharmacology & therapeutics. 2020;52(1):143-54.
44. Olén O, Smedby KE, Erichsen R, Pedersen L, Halfvarson J, Hallqvist-Everhov Å, et al. Increasing Risk of Lymphoma Over Time in Crohn's Disease but Not in Ulcerative Colitis: A Scandinavian Cohort Study. LID - S1542-3565(23)00268-9 [pii] LID - 10.1016/j.cgh.2023.04.001 [doi]. (1542-7714 (Electronic)).
45. Lemaitre M, Kirchgesner J, Rudnichi A, Carrat F, Zureik M, Carbonnel F, et al. Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease. (1538-3598 (Electronic)).
46. Narous M, Nugent Z, Singh H, Bernstein CN. Risks of Melanoma and Nonmelanoma Skin Cancers Pre- and Post-Inflammatory Bowel Disease Diagnosis. Inflammatory bowel diseases. 2023;29(7):1047-56.
47. Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. Journal of Crohn's & colitis. 2017;11(6):649-70.

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Table 1. Characteristics at start of follow-up in the treatment cohorts: naïve (no treatment with thiopurines, tumor necrosis factors inhibitors (TNFi) and other targeted therapies), thiopurine (treatment with thiopurines), TNFi (treatment with TNFi), thiopurine+TNFi (overlapping treatment with thiopurine and TNFi), and treatment with vedolizumab, ustekinumab, and tofacitinib, in patients without a history of cancer

	Treatment cohort						
Characteristic	**Naïve**	**Thiopurines**	**TNFi**	**Thiopurines+TNFi**	**Vedolizumab**	**Ustekinumab**	**Tofacitinib**
Total	49 688	11 916	7 209	3 452	1 618	649	413
Sex, n (%)							
Female	24 403 (49.1%)	5 159 (43.3%)	3 231 (44.8%)	1 490 (43.2%)	729 (45.1%)	305 (47.0%)	174 (42.1%)
Male	25 285 (50.9%)	6 757 (56.7%)	3 978 (55.2%)	1 962 (56.8%)	889 (54.9%)	344 (53.0%)	239 (57.9%)
Age at diagnosis							
Mean (SD)	41.1 (18.1)	33.0 (16.2)	31.5 (14.4)	29.9 (14.3)	32.7 (16.3)	30.4 (14.4)	31.5 (13.6)
Median (IQR)	38.2 (26.9-54.0)	29.2 (20.6-42.9)	28.3 (20.8-40.0)	26.7 (19.3-38.3)	28.2 (20.2-41.9)	27.6 (20.0-38.4)	28.3 (21.3-39.9)
Categories, n (%)							
<18y	3 694 (7.4%)	2 038 (17.1%)	1 157 (16.0%)	705 (20.4%)	267 (16.5%)	120 (18.5%)	61 (14.8%)
18-<40y	22 803 (45.9%)	6 404 (53.7%)	4 255 (59.0%)	1 974 (57.2%)	913 (56.4%)	384 (59.2%)	249 (60.3%)
40-<60y	14 478 (29.1%)	2 479 (20.8%)	1 447 (20.1%)	626 (18.1%)	293 (18.1%)	113 (17.4%)	87 (21.1%)
≥60y	8 713 (17.5%)	995 (8.4%)	350 (4.9%)	147 (4.3%)	145 (9.0%)	32 (4.9%)	16 (3.9%)
Age at start of follow-up							
Mean (SD)	47.5 (18.3)	38.2 (17.1)	37.9 (15.6)	35.3 (15.1)	40.8 (17.3)	40.3 (15.6)	40.3 (14.6)
Median (IQR)	46.6 (32.8-61.5)	35.0 (24.7-50.5)	35.2 (25.6-48.8)	32.2 (23.6-45.3)	36.3 (26.8-53.5)	37.3 (27.5-51.0)	36.8 (28.4-49.6)
Categories, n (%)							
<18y	1 499 (3.0%)	1 154 (9.7%)	461 (6.4%)	336 (9.7%)	58 (3.6%)	19 (2.9%)	1 (0.2%)
18-<40y	17 497 (35.2%)	5 917 (49.7%)	3 859 (53.5%)	1 940 (56.2%)	844 (52.2%)	347 (53.5%)	236 (57.1%)
40-<60y	17 011 (34.2%)	3 240 (27.2%)	2 115 (29.3%)	891 (25.8%)	428 (26.5%)	198 (30.5%)	126 (30.5%)
≥60y	13 681 (27.5%)	1 605 (13.5%)	774 (10.7%)	285 (8.3%)	288 (17.8%)	85 (13.1%)	50 (12.1%)

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Education level (years), n (%)							
<=9	10 277 (20.7%)	2 264 (19.0%)	1 189 (16.5%)	618 (17.9%)	248 (15.3%)	104 (16.0%)	47 (11.4%)
10-12	22 634 (45.6%)	5 476 (46.0%)	3 373 (46.8%)	1 571 (45.5%)	739 (45.7%)	321 (49.5%)	201 (48.7%)
>12	16 593 (33.4%)	4 138 (34.7%)	2 629 (36.5%)	1 253 (36.3%)	628 (38.8%)	223 (34.4%)	165 (40.0%)
Missing	184 (0.4%)	38 (0.3%)	18 (0.2%)	10 (0.3%)	3 (0.2%)	1 (0.2%)	(0.0%)
Country of birth							
Nordic	45 054 (90.7%)	10 547 (88.5%)	6 315 (87.6%)	3 004 (87.0%)	1 415 (87.5%)	560 (86.3%)	375 (90.8%)
Non-Nordic	4 632 (9.3%)	1 368 (11.5%)	894 (12.4%)	448 (13.0%)	203 (12.5%)	89 (13.7%)	38 (9.2%)
Missing	2 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	(0.0%)	(0.0%)
Co-morbidity past 5 years, n (%)							
Diabetes mellitus[1]	2 761 (5.6%)	542 (4.5%)	299 (4.1%)	132 (3.8%)	94 (5.8%)	40 (6.2%)	17 (4.1%)
Ischemic heart disease[2]	1 221 (2.5%)	146 (1.2%)	66 (0.9%)	18 (0.5%)	17 (1.1%)	5 (0.8%)	2 (0.5%)
Hypertension[3]	11 593 (23.3%)	1 720 (14.4%)	977 (13.6%)	374 (10.8%)	321 (19.8%)	122 (18.8%)	64 (15.5%)
Chronic obstructive pulmonary disease[4]	249 (0.5%)	39 (0.3%)	15 (0.2%)	6 (0.2%)	6 (0.4%)	2 (0.3%)	1 (0.2%)
Cerebrovascular disease[5]	595 (1.2%)	64 (0.5%)	21 (0.3%)	9 (0.3%)	7 (0.4%)	3 (0.5%)	(0.0%)
Rheumatic diseases[6]	280 (0.6%)	66 (0.6%)	237 (3.3%)	36 (1.0%)	8 (0.5%)	15 (2.3%)	22 (5.3%)
Depression and anxiety[7]	9 965 (20.1%)	2 107 (17.7%)	1 534 (21.3%)	653 (18.9%)	407 (25.2%)	196 (30.2%)	104 (25.2%)
Medications during past 5 years, n (%)							
Drugs treating peptic ulcer and reflux	14 859 (29.9%)	5 437 (45.6%)	3 434 (47.6%)	1 660 (48.1%)	825 (51.0%)	340 (52.4%)	202 (48.9%)
Antidiabetics	2 877 (5.8%)	595 (5.0%)	336 (4.7%)	142 (4.1%)	100 (6.2%)	44 (6.8%)	20 (4.8%)
Non-steroid anti-inflammatory drugs (NSAIDs)	17 177 (34.6%)	3 291 (27.6%)	2 084 (28.9%)	877 (25.4%)	371 (22.9%)	156 (24.0%)	104 (25.2%)
Opioids	14 405 (29.0%)	3 687 (30.9%)	2 722 (37.8%)	1 168 (33.8%)	680 (42.0%)	296 (45.6%)	199 (48.2%)

[1] ≥2 main diagnoses of diabetes mellitus in the National Patient Register or ≥2 redeemed prescriptions for antidiabetic medications in the Prescribed Drug Register

[2] Hospitalization or ≥2 outpatient visits with a main diagnosis of ischemic heart disease from a Cardiology or Internal Medicine Clinic

[3] ≥2 redeemed prescriptions for antihypertensive medications in the Prescribed Drug Register

[4] ≥2 diagnoses in the National Patient Register

[5] Hospitalization or ≥2 outpatient visits with a main diagnosis of cerebrovascular disease from a Neurology, Stroke, or Internal Medicine Clinic

[6] ≥2 diagnoses in the National Patient Register

[7] Hospitalization or ≥2 outpatient visits with a main diagnosis of anxiety or depression in the National Patient Register or ≥2 redeemed prescriptions for antidepressants or anxiolytics in the Prescribed Drug Register

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Antihypertensives	12 838 (25.8%)	2 030 (17.0%)	1 220 (16.9%)	467 (13.5%)	380 (23.5%)	139 (21.4%)	72 (17.4%)
Lipid reducers	6 675 (13.4%)	1 080 (9.1%)	609 (8.4%)	253 (7.3%)	197 (12.2%)	79 (12.2%)	48 (11.6%)
Antibiotics	31 173 (62.7%)	7 740 (65.0%)	4 838 (67.1%)	2 306 (66.8%)	1 118 (69.1%)	466 (71.8%)	270 (65.4%)
Anticoagulants	7 918 (15.9%)	1 374 (11.5%)	926 (12.8%)	367 (10.6%)	318 (19.7%)	143 (22.0%)	79 (19.1%)
Drugs for obstructive airway diseases	8 407 (16.9%)	2 073 (17.4%)	1 305 (18.1%)	615 (17.8%)	340 (21.0%)	138 (21.3%)	80 (19.4%)
Antidepressants	9 501 (19.1%)	2 111 (17.7%)	1 501 (20.8%)	657 (19.0%)	407 (25.2%)	185 (28.5%)	108 (26.2%)
Anxiolytics	7 368 (14.8%)	1 652 (13.9%)	1 204 (16.7%)	503 (14.6%)	292 (18.0%)	141 (21.7%)	70 (16.9%)
Hypnotics, sedatives	9 149 (18.4%)	2 316 (19.4%)	1 647 (22.8%)	725 (21.0%)	465 (28.7%)	224 (34.5%)	123 (29.8%)
Montreal Stage at diagnosis/July 1, 2008							
E1 (ulcerative proctitis)	10 160 (20.4%)	768 (6.4%)	446 (6.2%)	168 (4.9%)	59 (3.6%)	22 (3.4%)	9 (2.2%)
E2 (left side)	10 872 (21.9%)	2 747 (23.1%)	1 575 (21.8%)	705 (20.4%)	325 (20.1%)	124 (19.1%)	86 (20.8%)
E3 (extensive)	15 343 (30.9%)	6 155 (51.7%)	4 094 (56.8%)	2 031 (58.8%)	1 086 (67.1%)	436 (67.2%)	299 (72.4%)
EX (extent not defined)	12 338 (24.8%)	2 241 (18.8%)	1 088 (15.1%)	548 (15.9%)	148 (9.1%)	66 (10.2%)	19 (4.6%)
Missing	975 (2.0%)	5 (0.0%)	6 (0.1%)	0 (0.0%)	(0.0%)	1 (0.2%)	(0.0%)
Primary sclerosing cholangitis, n (%)							
At diagnosis/July 1, 2008	1 103 (2.2%)	384 (3.2%)	237 (3.3%)	117 (3.4%)	81 (5.0%)	35 (5.4%)	16 (3.9%)
At end of follow-up	1 900 (3.8%)	598 (5.0%)	339 (4.7%)	177 (5.1%)	104 (6.4%)	39 (6.0%)	18 (4.4%)
Treatment before first diagnostic listing of ulcerative colitis/ July 1, 2008, n (%)							
5-aminosalicylic acid	37 405 (75.3%)	11 600 (97.3%)	6 949 (96.4%)	3 353 (97.1%)	1 586 (98.0%)	621 (95.7%)	408 (98.8%)
Colectomy	2 619 (5.3%)	633 (5.3%)	700 (9.7%)	302 (8.7%)	192 (11.9%)	106 (16.3%)	78 (18.9%)
Treatment during follow-up, n (%)							
5-aminosalicylic acid	34 378 (69.2%)	9 685 (81.3%)	5 103 (70.8%)	2 543 (73.7%)	1 027 (63.5%)	311 (47.9%)	240 (58.1%)
Vedolizumab	1 085 (2.2%)	1 289 (10.8%)	1 069 (14.8%)	646 (18.7%)	201 (12.4%)	33 (5.1%)	33 (8.0%)
Ustekinumab	486 (1.0%)	622 (5.2%)	609 (8.4%)	373 (10.8%)	242 (15.0%)	55 (8.5%)	47 (11.4%)
Tofacitinib	266 (0.5%)	345 (2.9%)	337 (4.7%)	211 (6.1%)	130 (8.0%)	41 (6.3%)	29 (7.0%)
Colectomy	1 374 (2.8%)	980 (8.2%)	626 (8.7%)	382 (11.1%)	170 (10.5%)	51 (7.9%)	24 (5.8%)

Abbreviation: TNFI, tumor necrosis factor inhibitor

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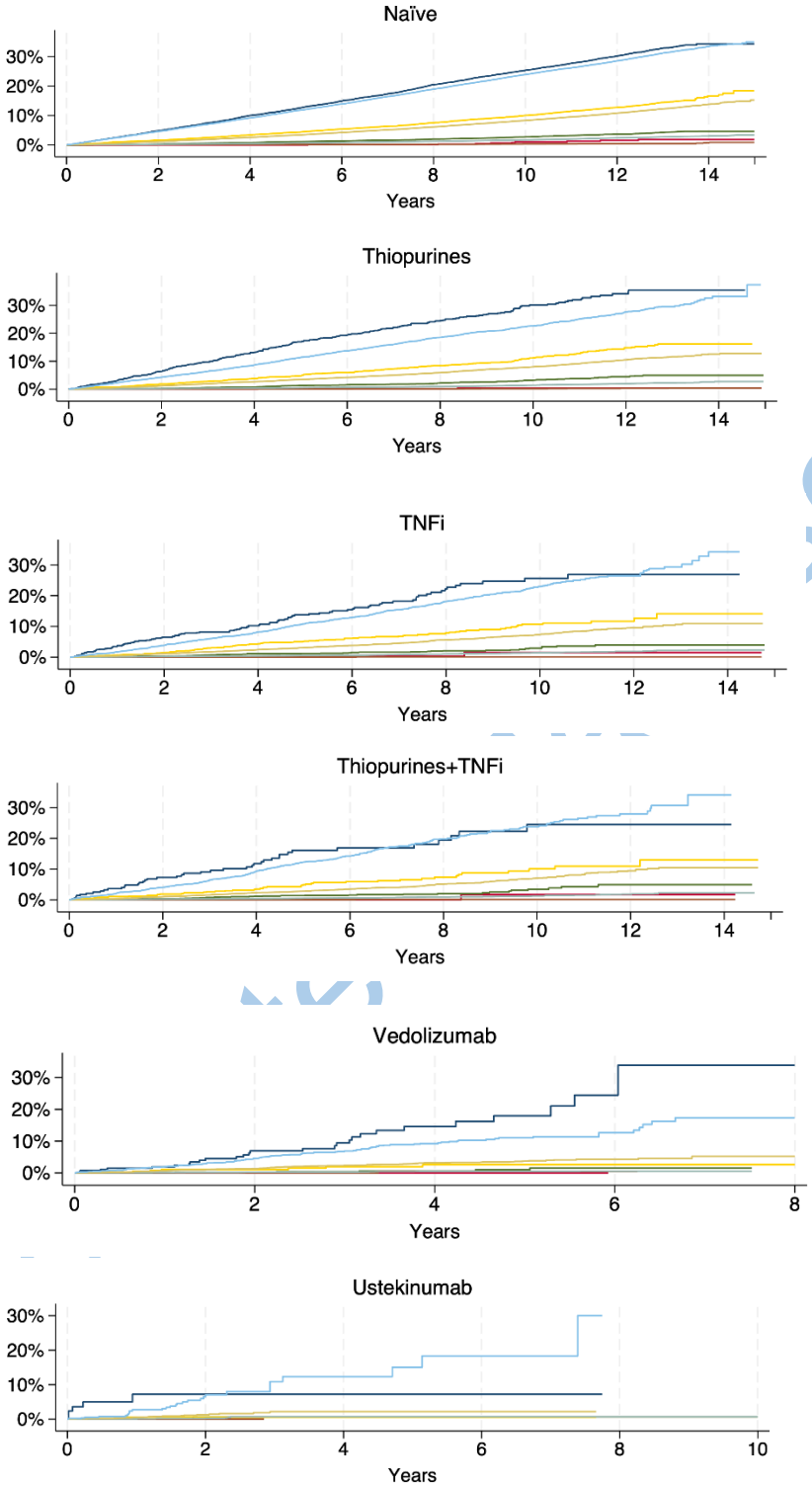

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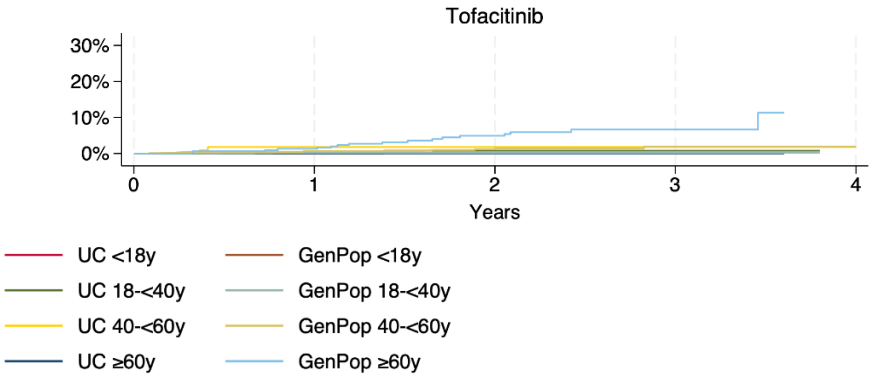

Figure 1. Time to any cancer in up in cohorts of patients with UC, stratified by age (<18y, 18 - <40y, 40 - <60y, ≥60y) and treatment at start of follow-up: Naïve (no treatment with thiopurine, tumor necrosis factor inhibitors (TNFi) and other targeted therapies), thiopurine (treatment with thiopurines), TNFi (treatment with TNFi), thiopurine+TNFi (overlapping treatment with thiopurines and TNFi), and treatment with vedolizumab (up to 8 years of follow-up), ustekinumab (up to 8 years), and tofacitinib (up to 4 years of follow-up)

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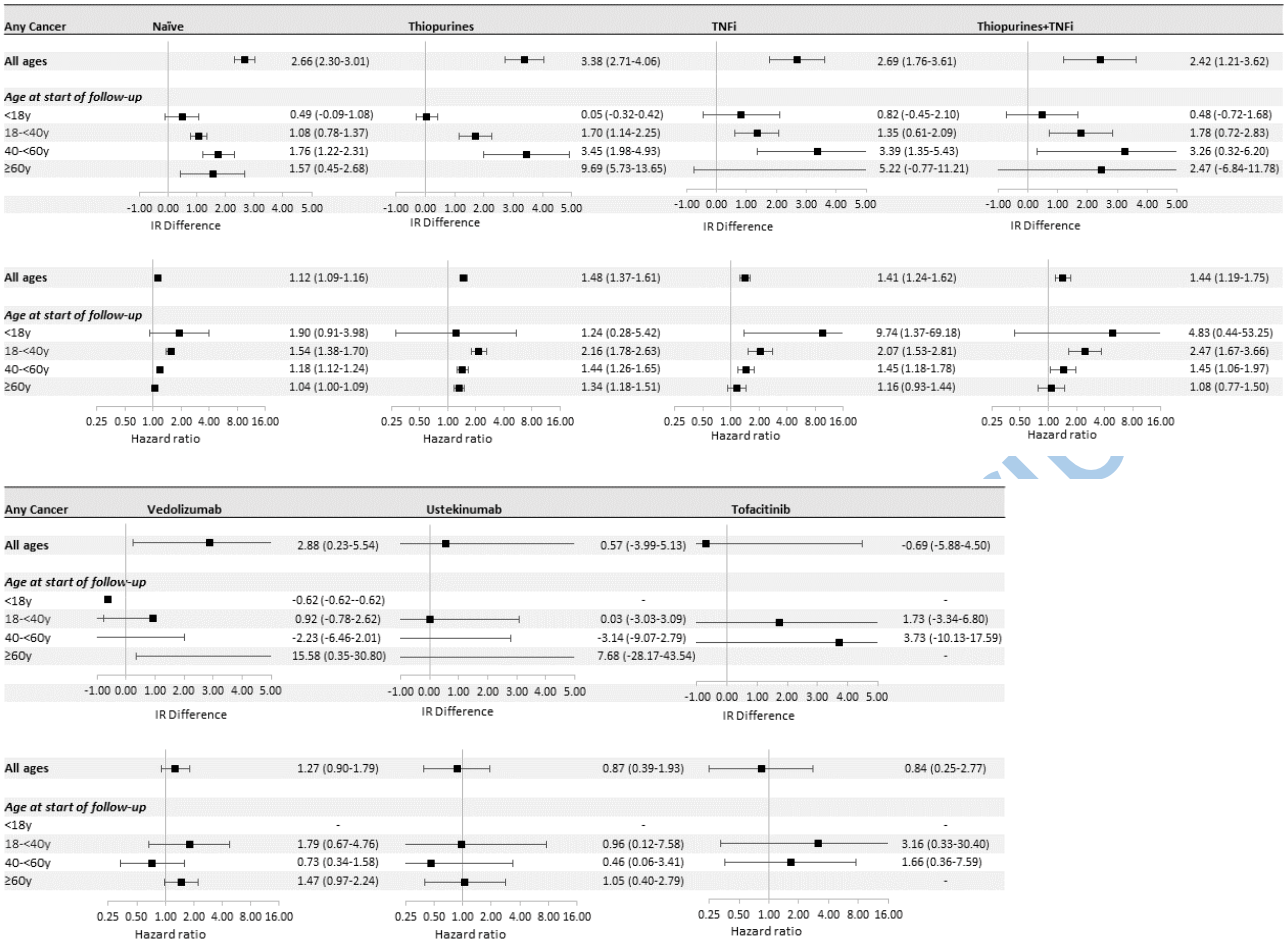

Figure 2. Incidence rate (IR) differences (cases/1000 person years) and hazard ratios with 95% confidence intervals (CIs) of any cancer in cohorts of patients with ulcerative colitis versus matched general population comparators, stratified by age (<18, 18 - <40, 40 - <60, ≥60 years) and treatment at start of follow-up: naive (no treatment with thiopurine, tumor necrosis factor inhibitors (TNFi) and other targeted therapies), thiopurines (treatment with thiopurines), TNFi (treatment with TNFi), thiopurine+TNFi (overlapping treatment with thiopurines and TNFi), and treatment with vedolizumab, ustekinumab, and tofacitinib

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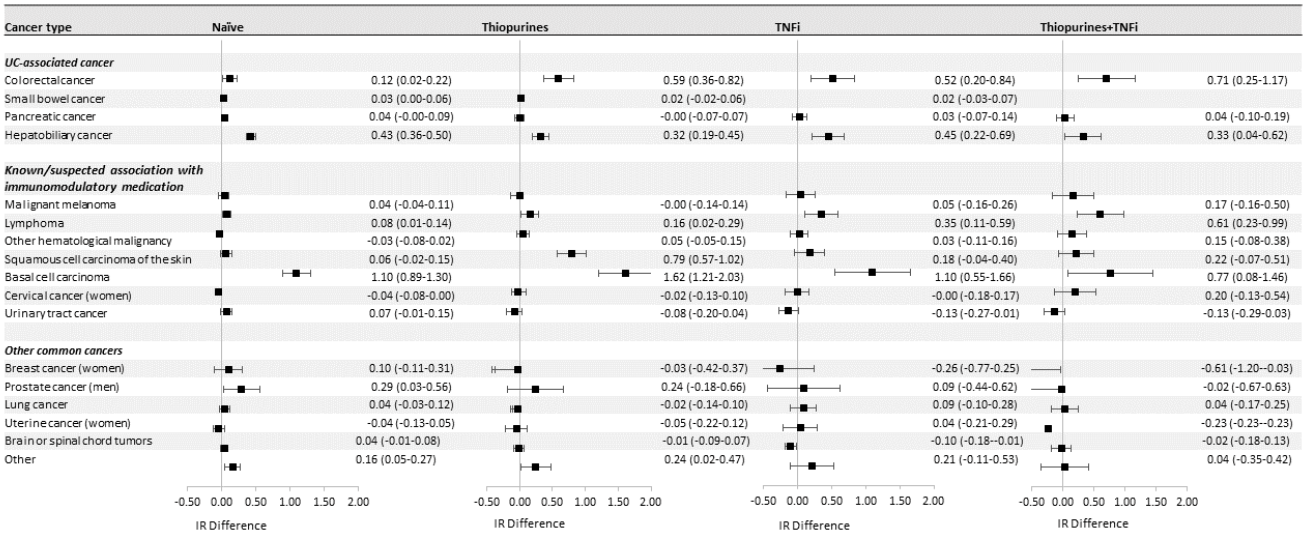

Figure 3. Incidence rate (IR) differences (cases/1000 person years) and hazard ratios with 95% confidence intervals (Cis) of of UC-associated cancers, cancers with known/suspected association with immunomodulatory, treatment, and cancers common in the population in cohorts of patients with ulcerative colitis versus matched general population comparators, stratified by treatment at start of follow-up: naive (no treatment with thiopurine, tumor necrosis factor inhibitors (TNFi) and other targeted therapies), thiopurines (treatment with thiopurine), TNFi (treatment with TNFi), and thiopurine+TNFi (overlapping treatment with thiopurine and TNFi)

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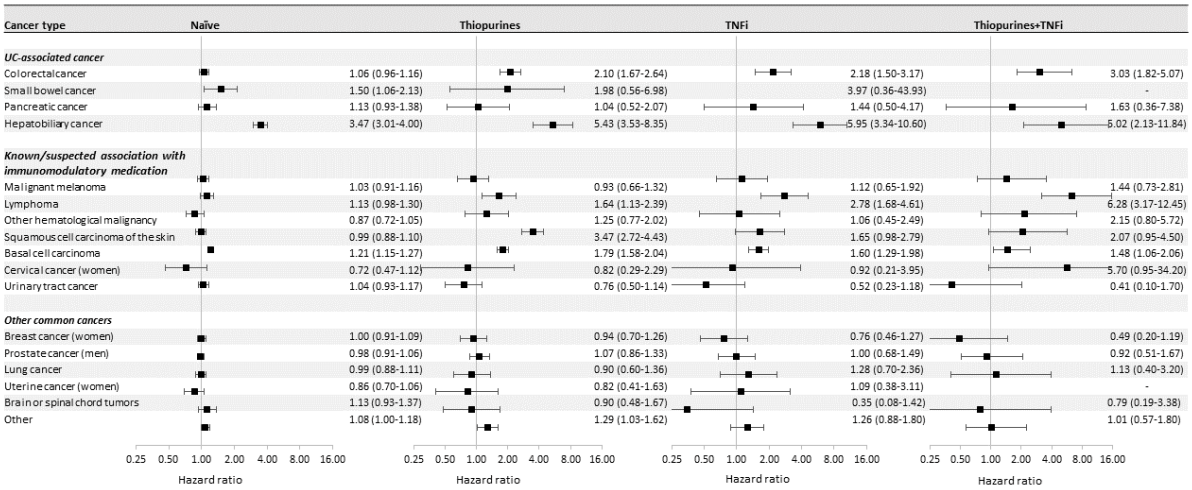

Figure 4. Hazard ratios with 95% confidence intervals (CIs) of of UC-associated cancers, cancers with known/suspected association with immunomodulatory treatment, and cancers common in the population in cohorts of patients with ulcerative colitis versus matched general population comparators, stratified by age (<18, 18 - <40, 40 - <60, ≥60 years) and treatment at start of follow-up: naive (no treatment with thiopurine, tumor necrosis factor inhibitors (TNFi) and other targeted therapies), thiopurine (treatment with thiopurines), TNFi (treatment with TNFi), and thiopurines+TNFi (overlapping treatment with thiopurine and TNFi)